Managing Hazardous Reactions and Compounds in Process Chemistry

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Managing Hazardous Reactions and Compounds in Process Chemistry

Jaan A. Pesti, Editor
NAL Pharmaceuticals Ltd
Princeton, New Jersey

Ahmed F. Abdel-Magid, Editor
Therachem Research Medilab
Birmingham, Alabama

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Foreword

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ACS Books Department

Foreword

One of the worst moments in my career as a process chemist happened in the early 1980s when we were, I think, on the 20th batch of a process operating at 2500L scale. The process was still under the direction of Process R&D, so two of us were covering the process 24 hours a day, working 12 hours a day. Nothing unusual in that I hear you say! But, on my shift, this batch started to exotherm from about minus 40, with full cooling on the vessel plus additional cooling from an external heat exchanger. I watched it with trepidation as the temperature slowly (fortunately!) climbed to nearly 80 degrees over an hour. We had also provided, during the emergency, additional cooling just to keep the temperature from rising so quickly and were relieved when the temperature eventually peaked and then began to fall. The decision point on whether to abandon the process, leave the building and allow the exotherm to take its course or stay and try to control it with extra cooling was not an easy one. It was based on rate of change of temperature and the fact that the temperature rise was relatively slow. But the process was still out of control.

The reason for such a strong exotherm occurring was that all the reagents had been added, but that we had not ensured, via an in-process measurement, that reaction was occurring, as it had in all previous batches. For some reason, there was a delay in the reaction initiation, such that when reaction occurred, all the reactants were in the vessel and we had lost control of the process. Clearly we hadn't done enough reaction and safety evaluation before scale up, but this was a pressure situation with material being needed very quickly, and the process had gone from lab to pilot plant to production in a few weeks. How many times have we heard this before? No time to do a thorough evaluation? This usually translates as a recipe for disaster!

A second incident a year later involving an uncontrolled exotherm with sodium hydride and DMF – a mixture which at that time was not thought to be hazardous – made me think much more clearly about the potential hazards of process chemistry, scale up and manufacture and how incidents involving loss of control and runaway reactions can be avoided. A more thorough safety evaluation procedure for processes prior to scale up was developed soon after and was alluded to in an early account that tried to delineate the principles of Chemical Development and Scale Up (*1*).

The subject of process safety then became an essential part of the training/continuing education courses that I taught when I set up my own company Scientific Update in 1989. When the journal *Organic Process R&D* was founded in the mid-1990s by the American Chemical Society, and I was asked to be editor, I realised that this new journal could be a vehicle for promoting process safety by publishing data re incidents that had previously occurred and the results of the subsequent investigation, trying to understand why they had occurred. Initially these snippets appeared in the Highlights from the Literature section but when we decided to have a special feature section devoted to process safety, then a team of reviewers was assembled to write a safety highlights section; this has continued as an annual feature. Safety also features strongly in my monthly Editorials and, on occasions, I have been critical of the lack of safety culture in some companies. When I was asked to write a book chapter covering the history of process chemistry a few years ago (*2*), process safety was also a key part of that chapter, since many of the principles of process safety that we now embrace only began to be established in the 1970s and 1980s, unfortunately after many occurrences of runaway reactions leading to loss of life or severe equipment damage.

Why is all this important? Because in most safety incidents there appears to be a lack of knowledge, and dissemination of knowledge of prior safety incidents and runaways can help in the education and training of new chemists and engineers. Hopefully this will lead to better process understanding, and you can't control a process from a safety viewpoint unless you understand it fully. Process chemists now have many tools and resources to help find out whether a pair of chemicals has any incompatibility, and there are many books to help chemists and engineers to understand how the design of a process can ensure that scale up hazards are minimised (*3–6*).

It therefore gave me great pleasure to hear that this new book "Managing Hazardous Reactions and Compounds in Process Chemistry" on the subject of process safety, both on the theory side and with case studies indicating the practical aspects, was in preparation. I have been privileged to read some of the drafts of the chapters and see that this new work fills a gap in the literature of process safety. I have no doubt that I and my colleagues, and hopefully others too, will use it in teaching courses on process chemistry, and that process chemists and engineers will find lots to educate and interest them in these well-written chapters. The editors have done a first class job in designing the themes, finding appropriate authors, and bringing the work to fruition. This is an up-to-date account of the state of the art of safety in a process chemistry context. I am sure all will enjoy reading and learning from the chapters.

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Trevor Laird
Scientific Update LLP
Editor-in-Chief
Organic Process Research and Development

Preface

Thirty years ago this December, the world witnessed in horror the unfolding of the worst disaster the chemical industry has ever known. In Bhopal, India, a combination of mishaps and faulty safety measures resulted in a chemical disaster on an unprecedented scale. On the night of the accident, a faulty valve had allowed one ton of cleaning water to leak into a storage tank containing 40 tons of MIC in the Union Carbide India Ltd. plant in Bhopal. MIC is an extremely toxic and low-boiling liquid (bp 40 °C) that reacts violently with water to produce a significantly large amount of heat (325 cal/g of MIC) and CO_2. Had the various safety interlocks originally installed still been present, possibly no hazardous situation would have subsequently developed. The safety vent gas scrubber designed to neutralize toxic discharges from the MIC storage system had been turned off for three weeks. In addition, a refrigeration unit that would have normally cooled the MIC storage tank had been drained of its coolant for use in another part of the plant. Thirdly, a gas flare safety system had also been out of action for the 3 months prior to the accident. As a result of a vigorous exothermic reaction of the MIC with water in the storage tank and the absence of functioning safety measures, pressure and heat began to rise rapidly. Finally, during the early hours of December 3, 1984, the safety valve gave way resulting in an explosion that spewed a cloud of the deadly MIC vapors into the air, drifting to the nearby densely populated residential area. The toxic material quickly killed an estimated 3800 people in the area adjacent to the plant. It further affected many thousands of people with injuries ranging from temporary to severe and permanent disabilities. Thousands of premature deaths reportedly occurred in the subsequent two decades. The true extent of the disaster will probably never be known.

The Bhopal tragedy served as a warning for the chemical and pharmaceutical industries. It is obvious that there was no effective emergency plan in place to deal with the disaster. The measures implemented to deal with such accidents were unavailable, inadequate, or faulty. This disaster motivated the authorities in many countries to implement laws and measures to stop similar accidents from happening again. The United States Congress passed the *1986 Emergency Planning and Community Right-to-Know Act.* The law requires companies to publicly disclose information about their storage of toxic chemicals so that citizens can identify the potential hazards that could cause harm or death. The

US Congress also established *the Chemical Safety and Hazard Investigation Board* (CSB) in 1990, which became operational in 1998. The CSB has a mission to investigate and determine the root causes of chemical accidents to prevent future occurrences and provide education to prepare for, prevent and respond to chemical accidents. Similar measures were taken in the European Union and the UK. Today, the industry has a better understanding of the importance of safety and controlling potentially hazardous reactions.

The potential for hazards and accidents always exists when we carry out a chemical reaction, even on a small scale in a chemistry laboratory. Some of the potential hazards emanate from the exothermic nature of many of the chemical reactions. In exothermic reactions, energy is released to the surroundings, and for safe operations several measures, independent and orthogonal, should be in place to control this energy release, particularly under atypical operating conditions. In the absence of these controlling measures, the reaction temperature will rise and typically the rate of reaction will increase, further raising the temperature. This vicious cycle may result in a runaway exothermic reaction and decomposition that exceeds the capability of a cooling system. Sudden increase in volume and pressure may also result, which may lead to explosions and fire. Other hazards originate from the toxic effects of a reagent, reactant or product. Such hazards cause undesirable health effects and occasionally fatal accidents. The reaction waste may combine many hazards such as toxicity in addition to explosion and fire hazards potentials. Scaling up chemical reactions to the pilot plant and manufacturing scales greatly multiplies the hazardous effects and increases the dangers associated with chemical reactions. For instance, what was observed as a mild exothermic reaction in a laboratory scale may become an uncontrolled runaway reaction on a large scale. Noticeable gas evolutions at 100 mL scale may become explosion hazards in the plant that can lead to a disaster.

Understanding the thermal behaviors of chemical reactions give us the tools to anticipate and manage chemical hazards. In order to make a profound safety assessment, it is essential for chemists and engineers to know the characteristics of a chemical reaction, including heat generation, gas production, and the thermal stability of all substances or mixtures used and produced in reactions. The identification and analysis of all possible risks allows for better planning and management of potentially hazardous chemical reactions and particularly for avoiding runaway reactions. When we better understand the thermal nature of chemical reactions, we can design chemical and engineering solutions that will allow us to safely use and synthesize potentially hazardous reagents and products. While an experienced chemist can usually identify potentially dangerous reagents and reactions, this is not a reliable method for their determination. Identification of potential hazards in a chemical reaction is carried out by screening and thermal analysis of reactions using calorimetric methods such as differential scanning calorimetry (DSC) and accelerating rate calorimetry (ARC). Quantitative thermal analysis using these calorimetric methods gives a better understanding of potential thermal hazards and the means of designing and implementing the safety measures necessary for preventing them. The continued growth of the chemical and pharmaceutical industries is contingent on implementing advanced safety measures and new technologies to eliminate or minimize the potential dangers associated with development and scaling up of chemical reactions.

We are introducing this book on the understanding and management of hazardous reactions and compounds in process chemistry at all stages of development and production. It coincides with the 30th anniversary of the Bhopal tragedy to remind us that while our discipline has achieved great advances in the science and engineering of reaction safety, we must not be complacent. Most companies have dedicated departments and professionals who analyze chemical reactions for possible hazards using cutting edge science and technology tools. Companies without such resources can make use of contract companies that will perform this work. They can assess the dangers and recommend solutions.

This book contains 16 chapters written by some of the most noted and accomplished professionals in this field. The chapters cover topics on conducting safely traditional batch reactions, semi batch reactions and continuous flow reaction techniques. We have divided the book into three sections that are highlighted below.

The first section titled *Philosophy of Safe Process Chemistry* is related to strategies and protocols of handling potential hazardous reactions. The opening chapter of this section is written by **Danny Levin** of Norac Pharma. His chapter is particularly interesting to anyone involved in chemical safety and presents an overview of what changes when a reaction is scaled up and especially what can go wrong and why. He carefully illustrates his points with calculations and examples of known disasters to derive useful lessons and enlightenment for process scientists, engineers and anyone scaling up chemistry. Also, don't miss the delightful drawings by his daughter that illustrate the chapter! **Tony Zhang** of the Small Molecule Design and Development group at Eli Lilly, and a fellow board member of *Org Process Research & Development*, along with **Sean P. Lapekas**, discourse on the DNA of safety by cleverly weaving a metaphorical parallel of Quality by Design to Safety by Design. By examples and demonstrating how concepts used in other industries relate to chemical safety, they convince the reader that safety must be considered as a process is designed, not as an afterthought when kilogram scale is being contemplated. **Steven Stefanick** of Janssen Pharmaceutical Research and Development LLC has had long experience at Johnson and Johnson on designing safe reactions for the process group — one of the reasons why J&J's safety record has been so admirable over decades. He describes his part in designing the group's approach to conducting safe chemistry at the initial phases of research by highlighting several strategies, approaches and tools, as well as describing how this work then related to several examples. **Ryo Sugiyama** of the Takeda Pharmaceutical Company approaches safe process chemistry also by focusing on the initial stages of research, but places his emphasis on managing hazardous reagents rather than substrates. As any scientist knows, there are thousands of chemicals we use that can lead to fires and explosions, and understanding the limits of their safe use is critical if you wish to rapidly scale up a new reaction. **Thomas Archibald**, a consultant with many years of service to process chemistry and engineering, has written an all-encompassing manual of how to conduct azide chemistry from cradle to grave, an excellent resource for anyone contemplating on running azide chemistry at any scale. All aspects from designing the work space to waste disposal are covered in this detailed manual of running safe azide chemistry.

The second section of the book contains descriptions of the development of successful examples of hazardous process chemistry titled *Examples of Holistic Process Development with Focus on Safety*. **Joerg Deerberg**, of Bristol-Myers Squibb leads off this section describing the process development that allowed two hazardous reactions to be safely run on route to a multi-hundred kilogram synthesis of saxagliptin, BMS and AstraZeneca's new oral hypoglycemic drug. This is a particularly good example of the value of teams dedicated to examining the thermochemical properties of a process and then deriving the limits and required precautions of the resulting large scale work. **Stefan Abele** of Actelion Pharmaceuticals Ltd, another fellow board member of *Org Process Research & Development*, describes his group's work in defining the safe limits for chemistry related to Diels Alder reactions leading to potential pharmaceutical entities. He explains the execution of a carefully planned program to understand the potential risks and generates extensive data that lead to his group's conclusions for safe processing. The work incorporates numerous factors important to safety in industrial pharmaceutical development. **Noel A. Hamill** and **Mark E. Howells**, of Almac Sciences and Novozymes A/S, respectively, write about their experiences in the safe management of hazardous reagents and reactions over six case studies, integrating the numerous factors necessary for safe but efficient processing. They also provide an introduction that generates lucent understanding of how to approach safety in an industrial lab setting that derives from their extensive familiarity of the field. **James H. Simpson** of Bristol-Myers Squibb describes his group's scale up to kilogram scale synthesis of potentially explosive ethyl diazoacetate, required for use in the synthesis of a potential drug. By a logical and systematic approach to development, and extensive use of analytical tools for thermal understanding of the reactions, his team improved the chemistry and prepared several >100 kg batches safely in time to allow the project to proceed. **Nicholas A. Straessler** of ATK Aerospace Group writes of the development and safe handling of an energetic anti-cancer agent. He first presents a useful guide and general commentary for working under nitration conditions and the proper techniques for processing and handling energetic materials. The second half is a fascinating story of how even a compound with multiple nitro groups and a strained azetidine ring can be safely prepared and handled as long as calorimetry is effectively used to establish chemical guidelines and precautions are maintained. **Oliver Thiel** of Amgen describes his group's development of an alternative means to access a key intermediate focused on first achieving a fit-for-purpose protecting group switch to eliminate the use of the hazardous *p*-methoxybenzyl chloride, and later engineering out the protecting / deprotecting steps to derive a safe, efficient and short synthesis of their desired target. Skillful use and interpretation of various calorimetric analytical tools maintained all safety decisions on a rigorous scientific basis.

The final section is named *Safe Process Chemistry through Continuous Processing* and contains examples of continuous processes and flow chemistry. Leading off this section is an extensive review by **David Ager** of DSM on how to utilize flow chemistry to handle hazardous reagents, intermediates and reactions.

It is remarkable how this field has progressed dramatically in a few years, and David has composed a comprehensive review that would be an excellent place to start a literature search for nearly any reaction that has been run in flow. **Ayman Allian** of AbbVie discusses the rarely used reagent ozone in flow. Ozone is a classic means for cleaving olefins in a green and cheap fashion but is rarely used for safety reasons on large scale. Ayman demonstrates how a well-designed continuous processing protocol can be safely crafted by using FTIR to completely monitor the various oxidation reactions to ascertain safety at all steps. Later for large scale work, a continuous bubble reactor was fabricated that permitted continuous operation and good mass transfer of the gas to liquid phase. **Bryan Li** and **Steven Guinness** of Pfizer Chemical R&D review two case histories from Pfizer that detail the use of flow to circumvent the explosive hazards of diazonium salts and the handling of lithium hydride, both insoluble compounds in the solvents used in flow. Usually charging or creating reactive solids in a flow apparatus present significant problems for safety as well leading to inconvenient plumbing problems, however the Pfizer researchers solved the problems and developed processes that could have been used commercially. **Leslaw Mleczko** and **Dongbo Zhao** of Bayer give a background perspective on the development and use of Micro Reactor Technology (MRT) to solve a low temperature lithiation problem, in this case for a reaction that essentially cannot be done in batch safely. In addition to their work, they also deliver a comprehensive review to the use of flow to handle organolithium reactions in a safe manner. Finishing off the book is a chapter by **Sri Venkatraman** and **David Lathbury** of AMRI and Astute respectively, who present two examples of reactive and potentially hazardous chemistry whose problems were neatly solved by going to flow. One project circumvented problems involved with ring metallation and carboxylation to allow processing of 22 kg of material, and the other involved a Pd catalyzed α-arylation reaction that could easily run away

We gratefully acknowledge the many people whose dedication, hard work and expertise in their fields made this book possible. Our thanks to all the authors, the ones listed above as well as the coauthors who are acknowledged in the individual chapters. Their valuable contributions and hard work are greatly appreciated. We greatly appreciate the work of our referees who made valuable suggestions for improvement. Many thanks to our colleagues at the ACS Books who encouraged and facilitated the compilation of this book: Tim Marney, Bob Hauserman, Nikki Lazenby, and Arlene Furman. Neal Anderson helped us review parts of the book and we thank him for useful discussions. A special thanks to Trevor Laird whose foreword elegantly states the importance of the dissemination of safety information and whose work at *Org Process Res & Dev* and Scientific Update has promoted safety in our industry more than any other single scientist.

We were motivated to create this book by our appreciation throughout our careers in chemical process research of the importance of reaction safety. We believe a successful process is in the first place a safe process. We are producing this book in the hopes that we might influence scientists and engineers to craft safe chemical processes that avoid dangerous situations and perhaps even save a life. We hope the readers find this book to be a useful addition to the other publications in this field. We assembled a collection of unique topics by top and experienced professionals from leading organizations, hoping the readers will find it to be a useful reference and a valuable resource for conducting safe operations in the laboratory and in the plant. In addition to its scientific value, we think the book is also entertaining and good reading — a tribute to the great job of the talented authors.

Jaan A. Pesti
NAL Pharmaceuticals Ltd
7 Deer Park Drive
Princeton, NJ 08852
pesti-office@oprd.acs.org (e-mail)

Ahmed F. Abdel-Magid
Therachem Research Medilab, L.L.C.
196 Highland View Drive
Birmingham, AL 35242
afmagid@comcast.net (e-mail)

Editors' Biographies

Jaan A. Pesti

Jaan A. Pesti was born on Long Island, NY in 1954. He received his Bachelor's degree from Long Island University, Brooklyn NY in 1976 and his Ph.D. in organic chemistry from Columbia University in 1981. Following postdoctoral research in synthetic organic chemistry at University of California, Berkeley from 1981–1983, he joined the staff of Dupont's Medical Products Division in Wilmington, DE and Deepwater, NJ, conducting research in process development from bench scale to pilot plant manufacture. He later transitioned to Dupont Merck Pharmaceuticals, Dupont Pharmaceuticals, joined Bristol-Myers Squibb Pharmaceuticals in 2001, and is currently a Director at NAL Pharmaceuticals.

His career has focused on the process development of potential drugs and medical devices, including contributing to the processes to manufacture the marketed drugs losartan and efavirenz. He has been the Associate Editor for the journal *Organic Process Research & Development* since 2008. He cofounded the conference series Balticum Organicum Syntheticum (BOS), held biennially in the Baltics since 2000, and the symposium series Process Chemistry: New Developments in Pharmaceutical Process Development held biennially at ACS National meetings.

Ahmed F. Abdel-Magid

Ahmed F. Abdel-Magid was born in Giza Egypt in 1947. He received his Bachelor's degree from Cairo University (Cairo-Egypt) in 1969 and his Ph.D. from Temple University (Philadelphia, PA USA) in 1980. After postdoctoral appointments at the University of South Carolina and SmithKline and French Laboratories, he joined Drexel University as Teaching/Research Associate in 1985 then as Adjunct Professor until 2006. He joined Wyeth Laboratories in 1986, Johnson & Johnson in 1987 and Therachem in 2009 where he holds the title of Chief Scientific Officer.

Organic Process Research was his focus for more than 25 years: he contributed to development of more than 50 processes including 5 for commercial manufacture of marketed drugs. He is the inventor of 23 issued US patents, editor of 3 books, and author of 85 publications. He was the executive officer and chair of the 39th National Organic Chemistry Symposium in 2005. He is currently the National Program Chair and a member of the Executive Committee of the Division of Organic Chemistry of the ACS. He is also a Patent Panelist for ACS Medicinal Chemistry Letters. His awards include the Philip B.

Hofmann Award for Outstanding Research from Johnson & Johnson (1994), the Philadelphia Organic Chemists' Club Award for outstanding contributions to organic chemistry (2007), the ACS-Philadelphia Section Award for conspicuous scientific achievement through research (2013) and he is a Fellow of the American Chemical Society (2009).

Chapter 1

Managing Hazards for Scale Up of Chemical Manufacturing Processes

Daniel Levin[*]

Norac Pharma, 405 S Motor Ave., Azusa, California 91702, United States
[*]Phone: (626) 334-2908; E-mail: dlevin@noracpharma.com

Scale up of chemical processes can introduce a variety of potential hazards including risk of thermal runaway and explosion. Many of these potential hazards are due to the deterioration in the ratio of surface area to volume that is suffered when manufacturing processes are operated at a larger scale than was used previously for labscale process development work. Such hazards can generally be mitigated by appropriate forward looking process design, anticipating the effects of scale up and ensuring effective control of significantly exothermic reactions by control of reactive reagent additions. A number of case studies are reviewed, along with supporting tools and resources, to illustrate how chemical reaction hazards associated with scale up should be identified and controlled. Other potential hazards, besides chemical reaction hazards, are also considered before the chapter concludes with a summary and some recommendations.

Introduction to Scale Up and Safety

Following tens of millions of years of natural selection and evolution, the two organisms depicted in Figure 1 are both well adapted to life within their respective niches. Consider though the very different ways that these two organisms have accommodated the basic processes that are essential to their lives on Earth. For example, how do they breathe and how do they regulate their body temperature?

In Managing Hazardous Reactions and Compounds in Process Chemistry; Pesti, et al.;

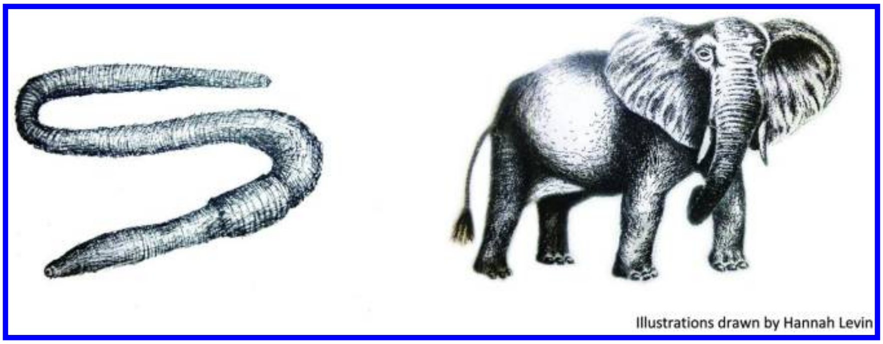

Illustrations drawn by Hannah Levin

Figure 1. Biological organisms of different scales

The earthworm “breathes” by passive gas diffusion through the surface of its skin, with oxygen diffusing into its body and carbon dioxide diffusing out of its body through its skin without forced ventilation. The elephant, by contrast, breathes by muscle-driven reciprocating bellows forcing air in and out of its lungs to facilitate gas exchange through the large surface area provided by alveolar sacs within the lung cavity.

The earthworm’s body temperature is essentially dictated by its environment, with temperature control achieved by temperature equilibration with the location where the worm chooses to situate itself. The elephant, meanwhile, uses its ears as radiators to dissipate heat, flapping them to facilitate air flow which serves to cool blood flowing through the ears.

So why does the earthworm manage to breathe and control temperature by passive diffusion of gases and heat, whereas the elephant needs to expend energy pumping air through its lungs and flapping its ears to achieve the same ends?

The answer (which will shortly bring us to the subject of safe process scale up for manufacture) is due to the very different surface area to volume ratios (or surface area to mass ratios) for the two creatures as a consequence of scale.

The surface area per unit volume for an earthworm is approximately 80 times that for an elephant (*1*, *2*). Now, the quantities of gases involved in respiration and the amount of heat generated by the creature are proportional to the molar quantities of the biological processes going on within each creature. That, in turn, is approximately determined by the weight or the volume of the creature. The high surface area to weight ratio for the earthworm means that it is able to rely on the surface area of its skin to achieve passive transport of heat and gases into and out of its body. For the elephant, however (with around 80 fold less surface area of skin per unit weight of body compared to the worm), the skin does not afford sufficient surface area for passive transfer of gases and heat into and out of its body. Hence the elephant has evolved to occupy and exploit its biological niche of huge size by active muscular transport of air into and out of its lungs (having high surface area alveoli for efficient gas diffusion), along with active dissipation of heat through the ears. The worm meanwhile is able to thrive with passive gas and heat diffusion through its skin.

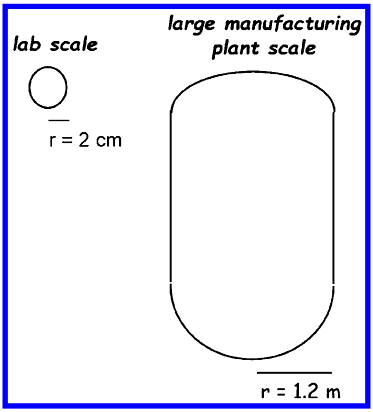
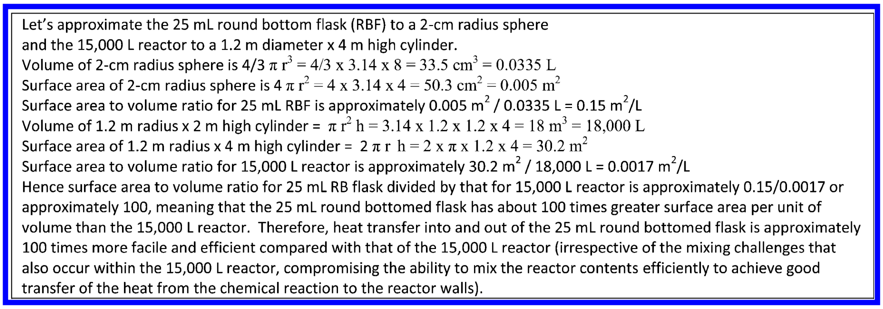


Figure 2. Contrasting scales of chemical reaction between a laboratory and a manufacturing plant reaction vessel.

The deteriorating ratio of surface area to volume on scale up of chemical processes has similar implications for the ability to remove heat from exothermic chemical reactions with increasing reaction scale and hence too for the ability to operate chemical reactions safely during scale up and at large scale.

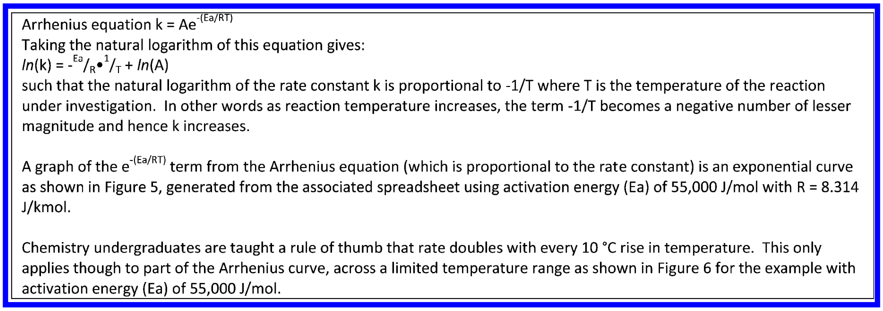
Contrast an exothermic reaction run in a 25 mL round bottomed flask (having diameter around 4 cm) compared with the same reaction run in a *circa* 15,000 L industrial reactor having diameter around 2.4 m (Figure 2). The amount of heat or gas evolved during the chemical reaction is proportional to the number of moles of the limiting reagent in the reaction mixture which (for a given concentration) is dictated by the volume of the reaction mixture. For a full, spherical reaction vessel, the volume is proportional to the cube of the radius of the vessel. The surface area for heat removal through the vessel walls, however, is only proportional to the square of the radius of the vessel. The surface area for disengaging gas from the reaction mixture across the surface of the reaction mixture is also proportional to the square of the radius of the vessel. So, as the scale of the reaction (along with concomitant quantity of heat and gas generated) increases proportional to the cube of the radius, the ability to remove heat and to disengage gas increases proportional to the square of the radius. Hence, it gets progressively harder to remove heat and gas as the reaction is scaled up. For example, it is approximately 100 times easier to remove heat from a 25 mL round bottomed flask than from a 15,000 L industrial reactor (see Figure 3).

The consequence of deteriorating surface area to volume ratio with increasing reaction scale is that an exothermic reaction perceived to demonstrate only a small exothermic temperature rise of just a few degrees Centigrade at laboratory scale can nevertheless equate to a dangerous, and even an explosive, safety risk at larger scale. This is because the heat loss through reaction flask walls with the large surface area to volume ratio at small laboratory scale means that heat of reaction energy can be readily dissipated through reaction flask walls at lab scale whereas the heat of reaction may not be adequately dissipated when the same reaction is run at large scale (where surface area for heat dissipation is much less relative to the volume of reaction mixture and relative to the quantity of heat produced). This can result in increasing reaction temperature on scale up and concomitant faster reaction kinetics at large scale, according to the Arrhenius equation (Figure 4), which can in turn lead to a vicious cycle of faster heat generation, further increasing temperature and ever faster reaction kinetics. Worse still is that the rapidly increasing temperature can also then provide sufficient energy to overcome the activation energy barrier for additional unwanted and potentially even more exothermic decomposition pathways. All of this can then lead to thermal runaway conditions (as temperature increases exponentially) and the potential for an explosion if the accelerating heat output vaporizes the reaction solvent or if gas is generated by decomposition at a faster rate than the gas can be released from the reaction vessel.



Let's approximate the 25 mL round bottom flask (RBF) to a 2-cm radius sphere
and the 15,000 L reactor to a 1.2 m diameter x 4 m high cylinder.
Volume of 2-cm radius sphere is $4/3\ \pi\ r^3 = 4/3 \times 3.14 \times 8 = 33.5\ cm^3 = 0.0335\ L$
Surface area of 2-cm radius sphere is $4\ \pi\ r^2 = 4 \times 3.14 \times 4 = 50.3\ cm^2 = 0.005\ m^2$
Surface area to volume ratio for 25 mL RBF is approximately $0.005\ m^2 / 0.0335\ L = 0.15\ m^2/L$
Volume of 1.2 m radius x 2 m high cylinder = $\pi\ r^2\ h = 3.14 \times 1.2 \times 1.2 \times 4 = 18\ m^3 = 18{,}000\ L$
Surface area of 1.2 m radius x 4 m high cylinder = $2\ \pi\ r\ \ h = 2 \times \pi \times 1.2 \times 4 = 30.2\ m^2$
Surface area to volume ratio for 15,000 L reactor is approximately $30.2\ m^2 / 18{,}000\ L = 0.0017\ m^2/L$
Hence surface area to volume ratio for 25 mL RB flask divided by that for 15,000 L reactor is approximately 0.15/0.0017 or approximately 100, meaning that the 25 mL round bottomed flask has about 100 times greater surface area per unit of volume than the 15,000 L reactor. Therefore, heat transfer into and out of the 25 mL round bottomed flask is approximately 100 times more facile and efficient compared with that of the 15,000 L reactor (irrespective of the mixing challenges that also occur within the 15,000 L reactor, compromising the ability to mix the reactor contents efficiently to achieve good transfer of the heat from the chemical reaction to the reactor walls).

Figure 3. Calculation of surface area to volume ratio change in scale up from a lab to a manufacturing plant

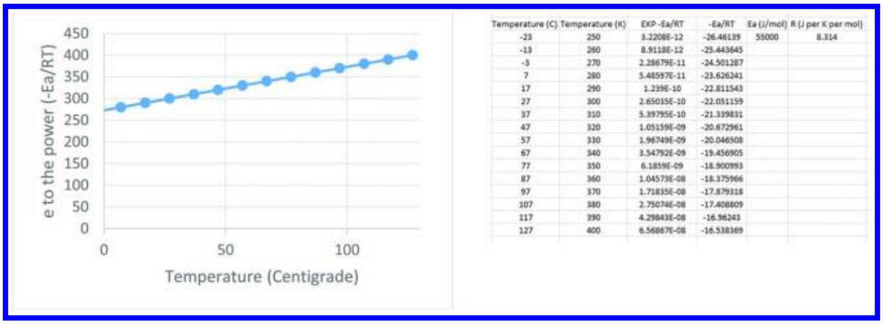


Arrhenius equation $k = Ae^{-(Ea/RT)}$
Taking the natural logarithm of this equation gives:
$ln(k) = -{}^{Ea}/_{R} \bullet {}^{1}/_{T} + ln(A)$
such that the natural logarithm of the rate constant k is proportional to -1/T where T is the temperature of the reaction under investigation. In other words as reaction temperature increases, the term -1/T becomes a negative number of lesser magnitude and hence k increases.

A graph of the $e^{-(Ea/RT)}$ term from the Arrhenius equation (which is proportional to the rate constant) is an exponential curve as shown in Figure 5, generated from the associated spreadsheet using activation energy (Ea) of 55,000 J/mol with R = 8.314 J/kmol.

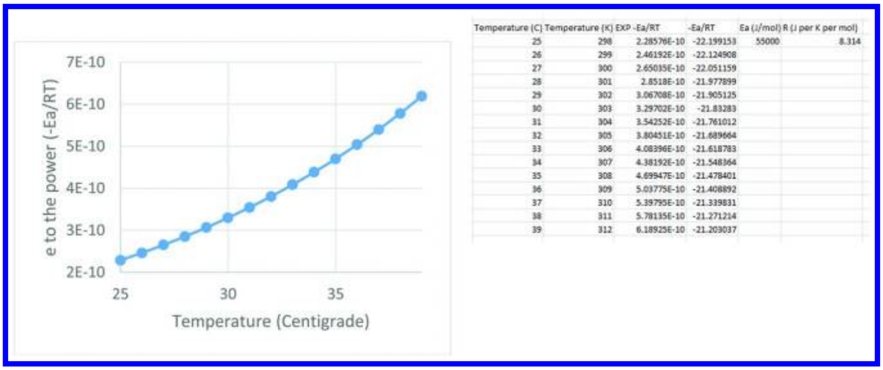
Chemistry undergraduates are taught a rule of thumb that rate doubles with every 10 °C rise in temperature. This only applies though to part of the Arrhenius curve, across a limited temperature range as shown in Figure 6 for the example with activation energy (Ea) of 55,000 J/mol.

Figure 4. Influence of temperature on reaction rate described by Arrhenius Equation



Temperature (C)	Temperature (K)	EXP -Ea/RT	-Ea/RT	Ea (J/mol)	R (J per K per mol)
-23	250	3.2208E-12	-26.46139	55000	8.314
-13	260	8.9118E-12	-25.443645		
-3	270	2.28679E-11	-24.501287		
7	280	5.48597E-11	-23.626241		
17	290	1.239E-10	-22.811543		
27	300	2.65035E-10	-22.051159		
37	310	5.39795E-10	-21.339831		
47	320	1.05159E-09	-20.672961		
57	330	1.96749E-09	-20.046508		
67	340	3.54792E-09	-19.456905		
77	350	6.1859E-09	-18.900993		
87	360	1.04573E-08	-18.375966		
97	370	1.71835E-08	-17.879318		
107	380	2.75074E-08	-17.408809		
117	390	4.29843E-08	-16.96243		
127	400	6.56867E-08	-16.518369		

Figure 5. Dependance of $e^{-(Ea/RT)}$ *vs. temperature across a broad temperature range*



Temperature (C)	Temperature (K)	EXP -Ea/RT	-Ea/RT	Ea (J/mol)	R (J per K per mol)
25	298	2.28576E-10	-22.199153	55000	8.314
26	299	2.46192E-10	-22.124908		
27	300	2.65035E-10	-22.051159		
28	301	2.8518E-10	-21.977899		
29	302	3.06708E-10	-21.905125		
30	303	3.29702E-10	-21.83283		
31	304	3.54252E-10	-21.761012		
32	305	3.80451E-10	-21.689664		
33	306	4.08396E-10	-21.618783		
34	307	4.38192E-10	-21.548364		
35	308	4.69947E-10	-21.478401		
36	309	5.03775E-10	-21.408892		
37	310	5.39795E-10	-21.339831		
38	311	5.78135E-10	-21.271214		
39	312	6.18925E-10	-21.203037		

Figure 6. Dependance of $e^{-(Ea/RT)}$ *vs. temperature across a limited temperature range where rate approximately doubles per 10 °C rise*

The problem can then be further exacerbated by deteriorating efficiency of mixing on scale up. This is because mixing is much more efficient at small lab scale than at large scale. Hence a reaction mixture is generally efficiently homogenized within just a few seconds at small lab scale but can take more than a minute or two to reach homogeneity at manufacturing production scale. Slower mixing on scale up therefore means that the localized concentration of an added reagent is higher around the region of addition at large scale than at lab scale, until the reagent mixes in. If the addition rate and reaction kinetics for addition of a reactive reagent (having significant heat of reaction) is faster than the mixing time at large scale then the localized high concentration of the added reagent can give rise to faster kinetics due to the higher concentration as well as a localized elevated temperature above the temperature of the bulk mixture. Slow mixing also diminishes the efficiency of dissipating the heat from the localized hot spot to the reactor walls for cooling. The consequences of these factors can give rise to further localized reaction rate, heat evolution acceleration and potential for localized thermal runaway, even if the bulk reaction temperature would not be expected to give rise to a thermal runaway. This risk of localized temperature excursion beyond the bulk reaction mixture temperature control parameters is why:

(i) intrinsic control of exothermic reaction progress (by means of controlled addition of one or more reagents at a rate slower than reaction rate), as well as
(ii) a substantive temperature safety margin between reaction temperature and thermal runaway onset-temperature

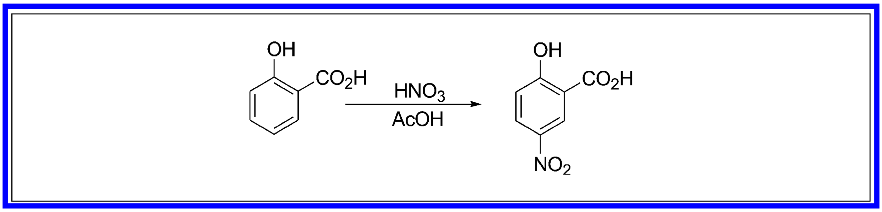
are both generally essential when performing significantly exothermic reactions, even if a reactor's control parameters are designed to hold the ***bulk*** reaction mixture temperature below the onset-temperature for thermal runaway.

Hence it is important, when scaling chemical reactions from laboratory scale to plant scale, to anticipate the effects of deteriorating surface area to volume ratio on scale up, adversely affecting mass transfer and heat transfer efficiency. This is necessary to ensure safe and controlled process operation at large scale. The rest of this chapter presents examples to illustrate this as well as describing tools to help with safety hazards anticipation and management.

Other sources of safety hazards are also considered, besides chemical reaction hazards, including operational hazards, toxicological and waste stream hazards. The chapter concludes with a short summary and recommendations.

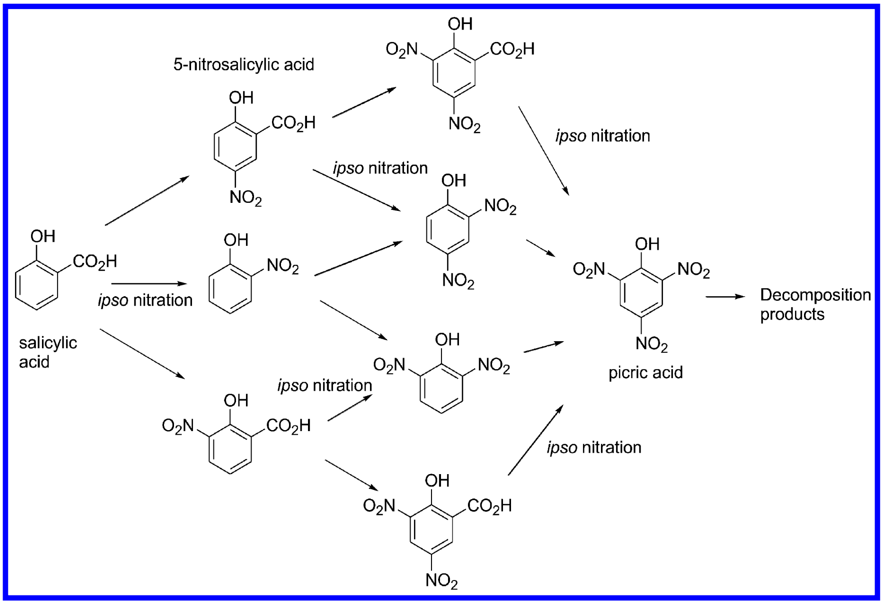
Nitration of Salicylic Acid: Understanding and Avoiding Exothermic Decomposition Leading to Thermal Runaway

The adverse impact of deteriorating surface area to volume ratio on process safety during scale up is demonstrated by the nitration of salicylic acid with nitric acid in acetic acid as solvent (Scheme 1) (*3*). This reaction may be run without incident at laboratory scale, employing slow controlled addition of nitric acid over approximately one hour with efficient cooling. However, the same reaction would likely give rise to a major plant explosion if the same one hour nitric acid addition profile were to be employed at larger manufacturing plant scale.



Scheme 1. Desired salicylic acid nitration reaction scheme

The reaction produces the desired 5-nitrosalicylic acid as the major product at lower reaction temperatures. However when the reaction is carried out at higher temperatures it can give rise to additional unwanted exothermic side reactions leading to over-nitrated products. This may then be followed by highly exothermic decomposition of the over-nitrated products and thermal runaway leading to explosion. The loss of reaction control at higher temperatures has been explained by Andreozzi and co-workers (*4*) to be due to a combination of over-nitrations, including *ipso* nitrations, ultimately generating 2,4,6-trinitrophenol (commonly known as picric acid, used historically as a military explosive) as depicted in Scheme 2. The picric acid that is generated is then prone to explosive decomposition as a consequence of escalating temperature from increasingly uncontrolled exothermic nitration reactions. A further potential concern arising from the use of acetic acid and nitric acid is the potential formation of acetylnitrate which is also explosively unstable in its own right (*12*).



Scheme 2. Nitration of salicylic acid. Reproduced with permission from reference (4). Copyright (2006) Elsevier.

The reaction temperature can be tightly controlled with relative ease at lab scale to prevent excursion to elevated temperatures and over-nitration products. However, when the reaction is run at large production scale, it is much harder to achieve efficient removal of heat and thereby to obtain a well-controlled and homogeneous reaction mixture temperature. As explained above, this is due to less surface area available for heat removal relative to increased reaction mixture volume, and more heat generated with less efficient heat transfer at large scale compared with lab scale, combined with less efficient mixing (less efficient mass transfer at large scale compared with lab scale). These effects result in increased localized concentration of nitric acid, as well as localized heat generation and elevated temperature in the vicinity of nitric acid addition at large scale. As a consequence of the longer time period to mix the region of highest concentration and greatest heat generation into the reaction mixture to bring it into contact with the cooling effects of the chilled reactor jacket.

We can further illustrate this scale up effect with estimation of scaled up heat transfer for the salicylic acid nitration into a 3,800 L glass lined mild steel reactor having heat transfer coefficient (U), estimated (*5*), to be around 160 W/m2.K and using the heat of reaction for the required nitration of -145 kJ/mol (*4*), with nitric acid addition over one hour. This shows that whereas the nitration might be safely accommodated at lab scale due to efficient heat transfer from reaction flask to ice bath at that scale, at a 3,800 L plant reactor scale with the same conditions as those used in the lab, the reaction could generate and detonate the equivalent explosive force of around 200 kg of TNT (Figure 7)!

The lab scale nitration procedure from Raiziss and Proskouriakoff[2] describes reaction of 100 g of salicylic acid (MW=138.1 g/mol, 0.724 mol) in 800 g of acetic acid (MW 60.05 g/mol, 13.32 mol) having SG 1.049 g/mL & volume of 763 mL, with 50 g of 98% fuming nitric acid (MW 63.0 g/mol, 0.778 mol) with SG 1.5 g/mL & volume of 33.3 mL, giving total reaction mixture volume of around 900 mL once all the nitric acid has been added.
The total heat evolved from the nitration in the lab scale reactor (assuming all added nitric acid gives heat of reaction of -145 kJ per mol) is 0.778 x 145 = **112.8 kJ** of heat, which we'll assume can be readily absorbed by use of an ice bath at lab scale to allow a safe low reaction temperature to be maintained throughout the 1 hour nitric acid addition.

Running this reaction in a 3,800 L glass lined mild steel plant scale reactor for which the useable working volume is around 3040 L (80% full) equates to a 3040 L/0.9 L = 3378 fold scale up from the lab scale reaction described above.
Thus heat generated by required nitration in the plant scale reactor = 3378 x 113kJ ≈ **380 MJ**.

The equation for heat transfer energy Q (measured in Watts) transferring through a material with heat transfer coefficient U between internal (reactor) with temperature T_r and external (jacket) with temperature T_j is:
$Q = UA (T_r – T_j)$
Where U = heat transfer coefficient between reactor contents and heating/cooling jacket ($W/(m^2K)$)
A = heat transfer area (m^2)
T_r = temperature within the reactor, i.e. the process operating temperature (K)
T_j = reactor jacket temperature (K)

So, for the 3,800 L glass lined mild steel reactor cooled by heat transfer fluid flowing through the reactor jacket assuming reactor jacket at 0 °C and reaction mixture at 20 ° C, with U = 160 $W/(m^2K)$, T_r = 20 °C, T_j = 0 °C and with reactor jacket area (in contact with the reaction vessel and through that the reaction mixture within the vessel) estimated to be 10 m^2, heat removal ability is calculated as follows:
Heat removal ability Q = 160 x 10 x (293-273) = 160 x 10 x 20 = 32,000 Watts or 32 kW

However, heat generated from the nitration reaction in the 3,800 L reactor with addition of the nitric acid at an even rate over 1 h (considering only the required nitration chemistry without any additional contribution from thermal degradation pathways and assuming rapid reaction kinetics controlled by rate of nitric acid addition) is around 380 x 10^6 J over 1 h.

As 1 Watt of energy production is defined as 1 joule per second = 3600 joules per hour,
the heat generated from nitration with nitric acid addition over 1 h (assuming temperature is not allowed to rise and generation and decomposition of picric acid is not initiated) = (380 x 10^6)/(3.6 x 10^3)= 105.6 kW.
This rate of heat output at 3,800 L scale is therefore 105.6/32 = 3.3 x the rate at which heat can be removed from reactor!

Hence if nitric acid is added over 1 h at 3,800 L plant scale with jacket temperature at 0 °C, the plant reactor cooling system would not be able to dissipate the heat generated by the required reaction quickly enough to maintain the temperature at 20 °C so that the reaction mixture temperature would escalate (since heat generated by the required nitration would exceed the rate of heat removal) which would then facilitate the unwanted over-nitration reactions at escalating temperature, leading to formation and highly energetic decomposition of picric acid with devastating consequences.

Picric acid formation requires 3 mol of nitric acid per mol of substrate so plant scale reaction could generate up to 0.778 x 3378 scale up factor / 3 = 876 mol of picric acid x MW 229.1 g/mol = 201 kg of picric acid,
equivalent to around 240 kg of TNT [since picric acid is reported[6] to have a relative effectiveness factor of 1.2 x the explosive demolition power of TNT). This is equivalent to the size of some of the larger conventional bombs dropped during WW2.

Note that this is a theoretical calculation, not backed up by practical experimentation or calorimetric measurements to determine safe operating boundaries so that it should not be relied upon as a determination of safe scale up conditions.

Figure 7. Theoretical calculation of heat of reaction from salicylic acid nitration

The calculation in Figure 7 only addresses the situation with full reactor cooling capability, whereas safe scale up should also accommodate the eventuality of reactor cooling system failure! Furthermore, the calculation assumes that nitric acid reacts as soon as it is added so that the heat of reaction is generated at a constant rate throughout the nitric acid addition. In practice however, the nitration reaction is acid-catalyzed so that the rate of nitration will initiate slowly and will increase as acidity increases throughout the nitric acid addition. Hence the heat flux generated by the nitration will increase through the course of nitric acid addition so that the calculated heat flux will be an overestimation at the start of nitric acid addition and an underestimation towards the end of nitric acid addition. The ability to control heat will likely therefore be even more difficult than that described through the latter stages of nitric acid addition.

Calorimetry is therefore essential to measure the actual heat flux generated through the course of a chemical reaction, as is measurement of the onset-temperature for thermal runaway which in this case would need to be checked for the reaction mixture at several time points through the course of nitric acid addition.

Finally, safety measures would also need to be defined to rapidly achieve safe conditions without the propensity for thermal runaway even in the event of cooling failure or other unexpected events.

These and other aspects of scale up are discussed further through the rest of this chapter. The point of this example is, however, that a reaction that may operate safely at small scale in the laboratory may nevertheless give rise to a catastrophic explosion and/or loss of containment when operated at a larger scale. This is because the ability to remove heat is compromised at large scale compared to lab scale due to the deterioration in surface area to volume ratio on scale up. It illustrates how large scale operation can access highly exothermic decomposition pathways that are not incurred with the more efficient heat removal, easier agitation, and better temperature control at lab scale. Hence lab scale success may well not be a reliable indicator of safety for larger scale operation of the same chemistry that worked safely in the lab!

T2 Laboratories Explosion and the Importance of Understanding Thermal Runaway Onset-Temperature

The previous example of scale up effects on safety with nitration of salicylic acid was considered from a theoretical perspective. This next example of an industrial catastrophe that actually occurred, caused by inadequate anticipation of scale up implications, is provided by the explosion and chemical fire at the T2 Laboratories plant in Jacksonville, Florida in 2007 that killed 4, injured 28, destroyed T2 Laboratories' facility, damaged buildings a quarter of a mile away and threw debris up to a mile away from the site of the explosion (see Figure 8, Figure 9, Figure 10, Figure 11).

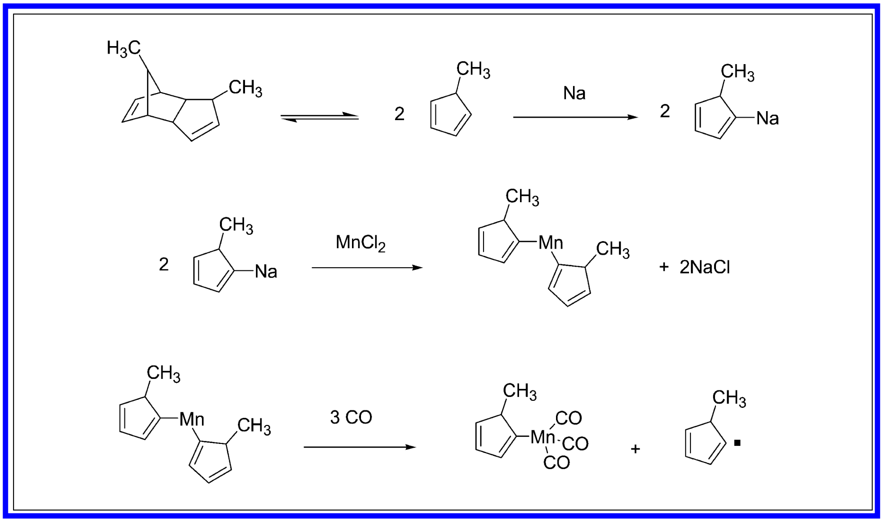
Figure 8. Aerial photograph of T2 site taken December 20, 2007 after reactor explosion. Photograph courtesy of U.S. Chemical Safety and Hazard Investigation Board, taken from Investigation Report No. 2008-3-I-FL, September 2009

Figure 9. JFRD responders in SCBA battle fire. Photograph courtesy of U.S. Chemical Safety and Hazard Investigation Board, taken from Investigation Report No. 2008-3-I-FL, September 2009 (see color insert)

Figure 10. Portion of the 3 inch thick steel reactor wall after T2 reactor explosion. Photograph courtesy of U.S. Chemical Safety and Hazard Investigation Board, taken from Investigation Report No. 2008-3-I-FL, September 2009

Figure 11. Portions of T2 reactor piping and agitator shaft embedded in surrounding areas caused by T2 explosion. Photographs courtesy of U.S. Chemical Safety and Hazard Investigation Board, taken from Investigation Report No. 2008-3-I-FL, September 2009

This tragic accident occurred when the T2 Company was operating a process for the manufacture of methylcyclopentadienyl manganese tricarbonyl (MCMT), a fuel additive used to increase the octane rating of gasoline in place of toxic tetraethyl lead (Scheme 3). The conclusions from the investigation by the U.S. Chemical Safety and Hazard Investigation Board (CSB) state that the explosion incident was caused by a deadly combination of inadequate means for both heat removal and relief of pressure, along with insufficient anticipation of the thermal runaway potential, coupled with a cooling failure during manufacture (*7*). This suggests a lack of adequate recognition of the magnitude of the heat and pressure that would be generated if the reaction mixture overheated sufficiently to cause thermal runaway. It also suggests insufficient study and understanding of the threshold temperature above which any such thermal runaway reaction would overcome efforts to keep the rate of reaction and heat evolution under control. Hence the dangers of reaction mixture overheating were underestimated or overlooked and insufficient backup measures were in place to provide additional cooling or quenching of the reaction mixture and pressure relief in the event of overheating. The consequence of this was that when the MCMT reactor cooling system failed, the T2 Laboratories staff were not able to prevent a thermal runaway, resulting in the uncontainable pressure generation and explosion.



Scheme 3. T2 synthesis of MCMT (8)

The chemistry being operated by T2 in the preparation of MCMT comprised metallation of methylcyclopentadiene followed by substitution of sodium by manganese and then carbonylation with carbon monoxide (Scheme 3).

The scale up safety problem with the T2 process originated from the lack of recognition that the specified reaction temperature was too close to the onset-temperature for an unwanted exothermic decomposition reaction. The de-dimerization and metallation of methycyclopentadiene by sodium metal in the first step required heating the reaction mixture in diglyme

($MeOCH_2CH_2OCH_2CH_2OMe$) to achieve the necessary reaction temperature of 177 °C, however a moderate further temperature excursion to 199 °C was sufficient to overcome the activation energy barrier for an undesired secondary reaction of the sodium metal with the diglyme solvent. Hence, when the cooling system on the reactor failed, the exotherm from the desired reaction brought the reaction mixture above the threshold temperature for thermal runaway due to the highly exothermic reaction of the sodium with the diglyme solvent. This led to a >100 °C per minute temperature rise and > 2000 atmospheres of pressure increase per minute which quickly overcame the pressure containment and relief capabilities of the reactor, resulting in the explosion.

The CSB estimated that the energy released by the explosion was equivalent to detonation of 1,400 pounds of TNT. The reactor was equipped with a pressure relief vent, but this was designed to only release pressure once 400 psi of pressure above atmospheric pressure was generated, but by the time this relief pressure was reached, the rate of pressure escalation was already so rapid that pressure relief through the pressure relief vent was inadequate to prevent rupture and explosion of the reactor. The CSB estimated that a lower pressure relief vent design, set to relieve pressure at 75 psi above atmospheric pressure, would have been sufficient to prevent temperature excursion above the thermal runaway temperature since that would have allowed the latent heat of diglyme solvent boiling to absorb the heat of reaction and prevent reaching the thermal runaway onset-temperature.

So, what could have been done to have better recognized and prevented the chemical reaction hazard risks? Probably the most important aspect would have been to better anticipate, or at least to test for, possible unwanted exothermic reaction chemistry that could occur within a potentially accessible temperature range of the intended operating temperature. It is generally sensible to ensure a safety margin of 100 °C or more between the planned reaction temperature and the onset-temperature for thermal runaway (although the T2 safety margin was only 199 °C – 177 °C = 22 °C) (*9*).

The temperature safety margin could have been assessed using thermal runaway onset determination calorimetry tools such as DSC or ARSST (*10*). The ARSST apparatus (see below) comprises a small scale calorimeter in a pressurized vessel (to prevent solvent evaporation) allowing measurement of heat evolution and pressure changes as the reaction mixture temperature is increased steadily through a controlled temperature ramp. It monitors for self-heating behavior which is indicative of a reaction exotherm, wherein the observed temperature rise rate of the reaction mixture exceeds the expected rise provided by the controlled linear temperature ramp from the instrument heat source. Once a thermal runaway is initiated, the internal temperature within the reaction mixture escalates steeply above the externally applied temperature, which is evident from temperature measurement by a thermocouple situated inside a small (*e.g.* 10 mL scale) reaction mixture flask. The CSB investigation showed an exponential temperature rise for the T2 Stage 1 chemistry, initiating from around 199 °C.

In addition to the practical determination of the onset of thermal runaway, it is also recommended to determine the heat of reaction and hence the worst case adiabatic (thermally insulated) temperature rise (equating to zero heat removal capability & accounting for the heat capacity of the reaction mixture) so as to estimate the temperature accessible by the reaction mixture without any cooling. In T2's case, although heating to 177 °C was necessary to initiate the required reaction, failure of the cooling system meant that the exotherm from the desired reaction was sufficient to heat the reaction mixture above the onset-temperature for thermal runaway (due to the unwanted reaction of sodium with diglyme). This was exacerbated by use of the pressure relief device designed to contain pressure up until 400 psi above atmospheric pressure. This allowed the solvent to superheat above its atmospheric boiling temperature sufficiently to access the thermal runaway onset-temperature without the compensating cooling contribution of solvent evaporation which could have mitigated the temperature rise before it was too late.

Had the risk of thermal runaway been recognized, a lower pressure relief setting of 75 psi above atmospheric pressure should have been sufficient to allow the desired reaction whilst also allowing solvent latent heat of evaporation to prevent superheating to the thermal runaway onset-temperature of 199 °C (since diglyme boils at 161-162 °C under atmospheric pressure and at a higher temperature under the elevated pressure of the reaction but low enough to prevent a temperature excursion to 199 °C).

Another important activity is to consider "what if" questions to anticipate, as far as reasonably possible, all adverse scenarios along with their potential consequences and mitigating steps that are appropriate where consequences are severe and the probability of occurrence is other than infinitesimally small (*11*). For instance, the risk and consequences of primary cooling failure on the MCMT reactor should have been better considered to identify backup cooling options in the T2 example.

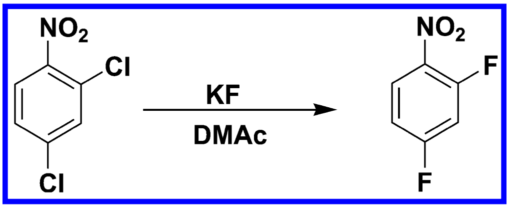
A useful source of reference is *Bretherick's Handbook of Reactive Chemical Hazards* for evaluation of chemical reaction hazard precedents pertaining to individual chemical reagents and combinations of reagents (*12*).

Having determined (*e.g.*, by ARSST study) the risk of thermal runaway onset at 199 °C, it would have been prudent to explore means to reduce the operating reaction temperature of 177 °C for the de-dimerization and sodium metallation process step of MCMT manufacture to realize a larger safety margin than the 199 °C – 177 °C = 22 °C temperature differential between reaction and runaway. It would also have been appropriate to engineer primary and secondary safety measures to preclude temperature excursion towards 199 °C by backup cooling systems and/or by engineering a reaction mixture dump to quench tank in the event of temperature rise above safe operating conditions.

UK Stanlow Explosion and the Importance of "What if" Consideration

Another example demonstrating the importance of considering "what if" scenarios, covering all possible undesired circumstances and their potential adverse consequences, is provided by the UK Stanlow explosion in 1990 (*13*, *14*) where 2,4-difluoronitrobenzene was being manufactured as an intermediate to 2,4-difluoroaniline which is in turn used as a chemical building block for synthesis of various agrochemicals and pharmaceuticals

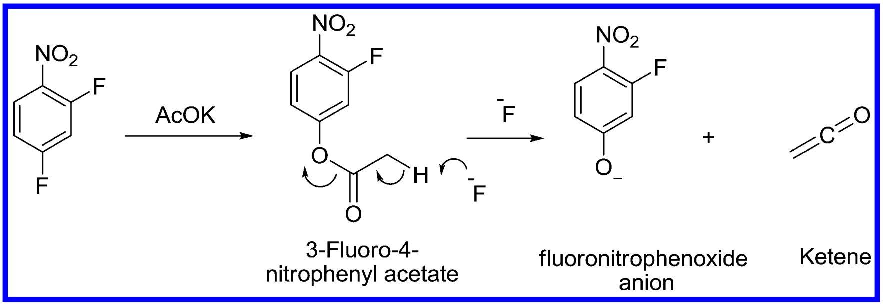
At Stanlow, 2,4-dichloronitrobenzene was reacted with potassium fluoride in the dipolar aprotic solvent dimethylacetamide (DMAc) at 165 °C. This solvent was necessary to achieve some degree of co-solubilization of both the organic substrate, 2,4-dichloronitrobenzene, and the inorganic potassium fluoride, to allow the two to undergo the required halogen exchange reaction (Scheme 4). Although nitroaromatics do generally demonstrate thermal instability, the chosen reaction temperature was considerably lower than any intrinsic decomposition thermal runaway temperature for the intended reaction mixture. Cost pressures prevailing for such relatively low value "fine chemical" building blocks however necessitate very efficiently optimized processes and minimal usage of all chemical materials, such that the Stanlow operation had also incorporated a solvent recovery and recycle stream to allow recovery and re-use of their DMAc reaction solvent.



Scheme 4. Fluorination of 2,4-dichloronitrobenzene by halogen exchange

As with the T2 explosion described previously, the Stanlow facility had demonstrated safe operation with many preceding batches before their explosion, but on 20th March 1990 their halogen exchange reaction mixture suffered a thermal runaway reaction, pressurization and explosion, unwrapping the reactor body into a flat plate, projecting plant shrapnel half a mile and injuring 7 employees one of whom died as a result of his injuries (*13*, *14*).

Subsequent investigation of the explosion demonstrated that the root cause was due to accidental water ingress into the recycled solvent stream from a leaking valve. This caused hydrolysis of DMAc to generate acetic acid which was not detected in the recovered DMAc solvent stream recycled back to the halogen exchange reactor. The acetic acid present in the solvent was then deprotonated by potassium fluoride (which is quite strongly basic under the essentially anhydrous conditions of the bulk dipolar aprotic solvent) (*15*) to form potassium acetate. Potassium acetate presumably participated in nucleophilic aromatic substitution with 2,4-difluoronitrobenzene to give rise to 3-fluoro-4-nitrophenyl acetate which was presumably also susceptible to deprotonation by potassium fluoride to liberate highly reactive and unstable ketene by *beta*-elimination of the relatively stable fluoronitrophenoxide anion, whose stability and good leaving group ability can be recognized by its relatively low pK_a estimated (*16*) at $pK_a = 6.4$ (Scheme 5). The ultimate cause of the explosion was presumably then the uncontrolled exothermic reactions of the highly reactive and unstable ketene unexpectedly generated as a reaction by-product resulting from the unintended introduction of water into the halogen exchange reaction medium *via* recycled DMAc, no doubt also thereafter accessing the decomposition onset-temperature of the nitroaromatic materials.



Scheme 5. Generation of energetic ketene by-product after hydrolysis of DMAc to acetate in halogen exchange reaction

Risk Assessment To Assist Focus on Process Aspects Requiring Risk Mitigation

A good practice in anticipating potential risks is to consider as many possible circumstances that could conceivably occur, for example by “brainstorming” (*17*) collective creative thinking. This should involve multidisciplinary participants covering all aspects of a chemical process (including chemists, chemical engineers, manufacturing staff, analytical scientists, and safety scientists) going through each step of an intended process, each piece of intended plant equipment, every process control step, all existing process safety related data and all possible external circumstances (including power failure, water failure, nitrogen gas failure, equipment failure, loss of containment, leakage between process streams and even lightning strike, tornado, tsunami or earthquake, if appropriate to the region) to identify every possible aspect that could go wrong, with *no* circumstance, no matter how unlikely, being off-limits. Critical review of suggestions is best deferred during this “brainstorming” phase of ideas generation so as to promote creative thinking.

Once all potential adverse circumstances are catalogued in this way, they can be prioritized by assigning to each a ***likelihood of occurrence*** (tabulated as probability, ***p***) and a ***severity of consequence*** (tabulated as severity, ***s***). The overall risk priority for each circumstance is then ranked by the product of ***p*** x ***s***, with the need for risk-mitigating steps and measures being needed:

- for all circumstances having serious potential consequences where probability is not vanishingly small, as well as
- for all circumstances where the product of probability and severity is high.

Where the magnitudes of potential consequences are not clearly understood, additional labwork research may be necessary for improved quantification. In the case of the UK Stanlow example above, it would probably not have been recognized that water could cause catastrophe. It would, however, have been appropriate to recognize the risk of water ingress *e.g.* from condenser water leakage, from wet solvent after workup leading to wet solvent recycle or from other equipment leaks or failures as well as the potential for DMAc hydrolysis to acetic acid. This could then have prompted questions as to what consequences water ingress or acetic acid presence could have on the process. Of course, the direct action of water on the halogen exchange reaction would inevitably have compromised yield and probably product quality as water would act as a competing nucleophile causing difluoronitrobenzene hydrolysis. This would then also then have led to HF formation which can (under bulk or localized acidic conditions) be highly corrosive and damaging to glass or steel reactor components, equating to a potential safety concern associated with plant construction corrosion and potential component failure. Consideration of the consequences of water ingress into the recycled solvent process stream should however also have prompted recognition that this could cause hydrolysis of dimethylacetamide during solvent recovery by distillation, or elsewhere within the process, especially when 2,4-difluoronitrobenzene was present. Although the adverse safety consequences of solvent hydrolysis to give acetic acid might not have been recognized, the ambiguity prompted by the question of "what could acetic acid do to the process" could have directed lab work to evaluate the effect of acetic acid on the halogen exchange reaction. It would have been appropriate for this work to have been done at small scale in an ARSST apparatus built to accommodate small scale thermal runaway and uncontrolled pressure increase reactions. Such a study would likely then have identified the catastrophic exotherm from acetic acid participation in the halogen exchange reaction, even if the mechanistic cause or prediction of the exotherm risk was not immediately recognized.

Having recognized the criticality of avoiding introduction of moisture and acetic acid into the halogen exchange reaction (for reasons of product yield, quality, plant integrity as well as process safety), steps could and should have been taken to monitor carefully for the presence of water and acetic acid in recycled solvent and in the halogen exchange reaction prior to solvent reuse and reaction initiation (for example by including a Karl Fisher test for water content and an adequately discriminating GC test for acetic acid). Reports of the Stanlow incident investigation describe that although water was involved in downstream processing (during product workup), the process was not designed to manage additional water ingress nor to detect acetic acid accumulation since the boiling temperature of the mixed acetic acid and DMAc was similar to that of DMAc alone and the GC method was unable to quantify acetic acid in the recycled DMAc (*13*, *14*).

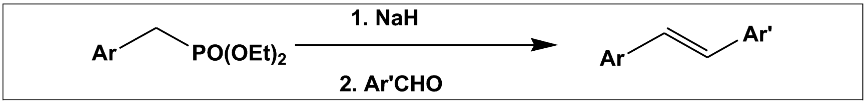
Chemists undertaking labwork for design of chemical processes should always be on the lookout for exothermic reactions. Such exotherms can be identified by chemical judgment, or by practical measurement, noting all increases in temperature (no matter how small) on reagent addition and subsequent reaction of those reagents, or by heat of reaction calculation (*e.g.* using CHETAH® software (*22*)), or (preferably) by operating chemistry within calorimetry apparatus designed to monitor and quantify heat of reaction (such as HEL Simular, Mettler Toledo RC1, OptiMax, or smaller scale EasyMax apparatus, Fauske ARSST and/or very small scale OmniCal differential accelerating rate calorimeter). As discussed above, any exotherm observed on small lab scale (even if only a couple of degrees) can give rise to a catastrophic event on large scale operation, especially if elevated temperatures facilitate unwanted exothermic decomposition or other reaction pathways.

As previously explained, this discrepancy (between lab and plant experience) is due to deteriorating surface area to volume ratio on scale up which results in decreasing efficiency in heat removal and hence heat retention, accelerating reaction rate with increasing temperature (as reflected by the Arrhenius equation), and potential for accelerating heat generation (thermal runaway), solvent vaporization and/or other gas generation, pressurization and explosion! Wherever possible, exothermic reactions should be controlled by regulated addition of the most reactive reagent, ensuring that this reagent is not added at a much faster rate than it can react. This is typically measured and confirmed by monitoring the heat generation or by reaction mixture sampling and analysis during process development.

A recurring misconception is that controlled slow addition of one or other reagent necessarily equates to reaction control and exotherm control. This is frequently not the case, however, and may not be recognized if evidence is not sought to confirm that slow reagent addition does indeed achieve exotherm control (if, for example, initial reaction rate is delayed through an induction period so that slow reagent addition nevertheless results in significant reagent accumulation before reaction). The issue is illustrated below with further examples; the first of these examples involves the Horner-Wadsworth-Emmons reaction and another (given later in this chapter) involves Grignard reagent preparation.

Horner-Wadsworth-Emmons Scale up safety Example Illustrating the Need for Reaction Control

In the case of a Horner-Wadsworth-Emmons (HWE) reaction to synthesize a diaryl olefin (Scheme 6), the chemists who carried out the initial process development work believed that they were diligently controlling their recognized reaction exotherm by adopting a careful slow addition of sodium hydride over 30 min at 0 °C to form the phosphonate stabilized anion, followed by careful slow addition of the aldehyde electrophile over 30 min at 5 °C to achieve the coupling reaction, before finally warming the mixture to 45 °C for workup.



Scheme 6. Horner Wadsworth Emmons synthesis of diaryl olefin

This procedure was tracked as part of process research and development work, using a Mettler Toledo MultiMax™ reaction system, only to find that in fact no reaction whatsoever had taken place throughout the slow controlled sodium hydride addition or the aldehyde addition, and that all of the requisite HWE reaction steps, comprising deprotonation, aldehyde coupling and phosphonate elimination, were in fact only taking place towards the end of the final warm up from 5 °C to 45 °C (*18*)! This was evident from the MultiMax™ tracking of heated and cooled reactor jacket temperature (T_j), in addition to the temperature of the reactor contents (T_r). The temperatures recorded for these two parameters (T_r & T_j) followed one another closely throughout all steps of the reagent additions, right up until completion of the final temperature ramp to 45 °C, with T_j and T_r only deviating widely after heating towards 45 °C (Figure 12). This deviation between T_j and T_r is because the MultiMax™ software was programmed to heat the mixture to 45 °C and to then hold it at 45 °C (T_r), however because the heat of reaction started to heat the mixture above 45 °C, when that temperature was reached and exceeded, the MultiMax™ control unit attempted to regulate the reactor temperature T_r back to 45 °C by applying cooling to the jacket (T_j) which was only successful in achieving the target T_r of 45 °C once the reaction had finished and the exotherm had subsided. The deviation between T_j and T_r (with T_r still rising despite cooling being applied to the jacket according to T_j) is indicative of the uncontrolled reaction exotherm when the heterogeneous sodium hydride base was finally able to react with the phosphonate to initiate the exothermic HWE reaction at around 45 °C.

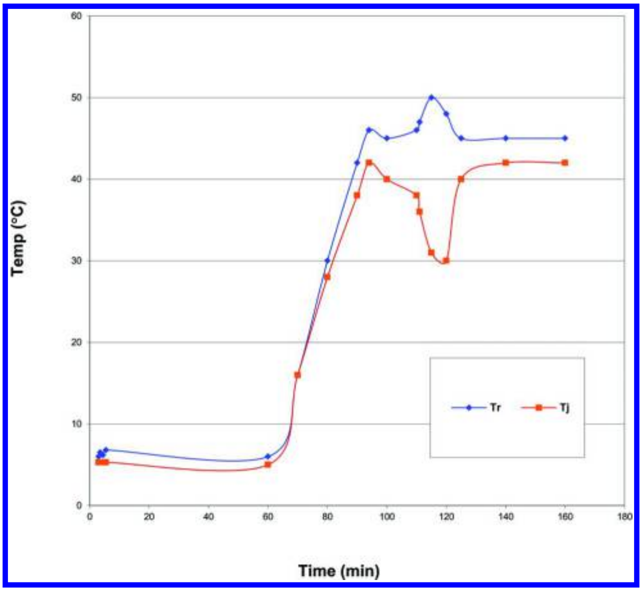


Figure 12. MT MulitMax™ temperature trace of reactor and jacket temperature for HWE reaction (see color insert)

This procedure was manageable at small lab scale due to the high surface area to volume ratio of the small lab reaction vessels used for early process development, allowing for easy and efficient reaction exotherm heat dissipation. Looking ahead though to large scale operation of this chemistry for commercial production of the target olefin (required for manufacture of a pharmaceutical product), it was clear that the procedure would be extremely dangerous on scale up. This is because the reaction did not actually commence until it was heated up to 45 °C at the end of the process such that all the reactive reagents were already present in the reactor prior to initiation of the exothermic reaction steps. Hence, once reaction commenced at a large scale, it would not be possible (due to poor surface area to volume ratio for heat removal through the large scale reactor jacket) to remove the heat of reaction as fast as it is generated. Under those circumstances the reaction mixture temperature would rise, causing reaction rate acceleration. Consequent heat generation and reaction rate would then further accelerate as would generation of hydrogen gas from sodium hydride reaction/decomposition, followed by solvent evaporation at an exponential rate. Further accelerating reaction and gas generation rate with increasing concentration would likely result in reactor pressurization since the exponential rate of hydrogen and solvent gas evolution would likely exceed the ability to safely vent the gases generated by the reaction. The worst case outcome could then be a reactor explosion and fire on ejection and ignition of the highly flammable hydrogen gas and solvent vapors. Of course, whether or not such a cataclysmic outcome could occur would depend on the precise scale and geometry of the reactor, cooling, and pressure relief system designs (in determining the point at which heat and gas evolution would overcome the ability to remove heat and release gas without pressurization).

Notwithstanding the likelihood or otherwise of a reactor explosion, it is also critical to ensure that evolution of significant reaction heat or gas are always under full control, since larger scale reactions operated with different temperature control to those adopted for smaller lab scale operation will likely give rise to different amounts of reaction by-products as temperature excursions may well facilitate alternative undesired reaction pathways.

The MultiMax™ data (Figure 9) provides a good illustration of how slow and controlled addition of one or other reagent does not necessarily equate to effective reaction control without also having data to demonstrate that (i) reaction kinetics, and therefore (ii) reaction heat evolution rate, ***are*** truly controlled by the regulated addition of a reagent. In the case of the HWE reaction, slow addition of each reagent in turn at temperatures below reaction initiation temperature simply facilitated accumulation of the full stoichiometric quantities of all reactive reagents that were then present in a metastable state ready to react, with no opportunity to control the extent and rate of reaction progress once it initiated. The problem of reagent accumulation without reaction during addition was due to the heterogeneity of the sodium hydride base in the solvent system and at the temperature adopted for the reaction such that the base was not able to interact with the phosphonate until a temperature of 45 °C had been reached. The solution to the problem (if you'll excuse the pun) was

(i) to use a homogeneous base solution in solvent (NaHMDS in THF) that was immediately reactive with the phosphonate substrate, and also
(ii) to add the base at a warmer temperature at which it reacted quickly and efficiently with the phosphonate without accumulation of unreacted base.

A common but generally misguided response by chemists to an exothermic reaction is to try to operate the reaction at a colder temperature than is ultimately required for an acceptable reaction rate, so as to try to balance the heat of reaction by the combination of cold reaction mixture heat capacity, combined with the heat losses that prevail at lab scale. This however typically leads to underestimation of the temperature rise that will occur at large scale (due to the deterioration in surface area to volume ratio on scale up). Colder addition (as with the HWE example above) can result in attenuated reaction rate and dangerous accumulation of unreacted reagent. Furthermore the approach of pre-cooling to absorb forthcoming reaction exotherm can also be potentially dangerous on scale up because reactions proceed faster the hotter they get (with increased rate of heat evolution for exothermic reactions). Hence reactions that are manageable with pre-cooling at lab scale (where significant cooling capability applies) can accelerate upwards in temperature, and heat output rate, faster at larger scale if heat capacity alone is unsufficient to absorb reaction exotherm without the additional heat losses that apply at lab scale.

The HWE reaction example presented here gives a good demonstration of the importance of choosing an appropriate temperature for addition of reactive reagents that is sufficiently warm for reagents to react immediately on addition.

With exothermic reactions capable of causing several degrees of temperature rise over a short period of time, it is important therefore to ensure that reactive reagent addition time is not so fast as to exceed heat transfer capabilities on scale up. The temperature at which reactive reagents are added must also not be so cold as to allow accumulation of unreacted reagents that can then give rise to an uncontrolled exotherm when reaction gets under way. Furthermore, reaction temperature and reagent addition rate should be optimized to ensure good selectivity for the desired reaction outcome. The heat of reaction for each portion of reactive reagent that is added at any one time should ideally be less than the achievable heat removal from reaction of that reagent portion, for safe temperature control (which is of course scale dependent), before a subsequent portion is added. Best of all is to ensure that each portion of a reactive reagent is reacted away as fast as it is added before a subsequent portion is added (with each portion size chosen to give a safely manageable temperature rise). This can be confirmed by monitoring the reaction mixture, for example using a rapid quench of reaction mixture samples to generate a new product that can be easily analyzed (*e.g.* by using a rapidly reacting electrophile to quench reaction mixture samples and allow measurement of unreacted reagent concentration present during reagent addition), or by using D_2O quench for NMR monitoring of reaction progress when anion formation is involved, or by using calorimetry as described below, or by using real-time reaction monitoring tools such as Mettler Toledo ReactIR™, or sampling, workup and HPLC analysis, for monitoring of materials that are in solution.

Reaction Calorimetry for Scale Up Safety Assessment

A very useful expedient is to measure and/or to calculate the heat of reaction (by calorimetry *e.g.*, using EasyMax™, or RC1 shown in Figure 13, or HEL Simular), and to then calculate the (worst case) adiabatic temperature rise, assuming no removal of heat whatsoever from the reaction mixture. This allows estimation of the worst case from scale up (aside from mixing effects) where cooling fails and/or where surface area to volume ratio is so bad that negligible heat is removed and all the heat of reaction serves to heat the reaction mixture. This is particularly important for reactions that are both rapid and exothermic.

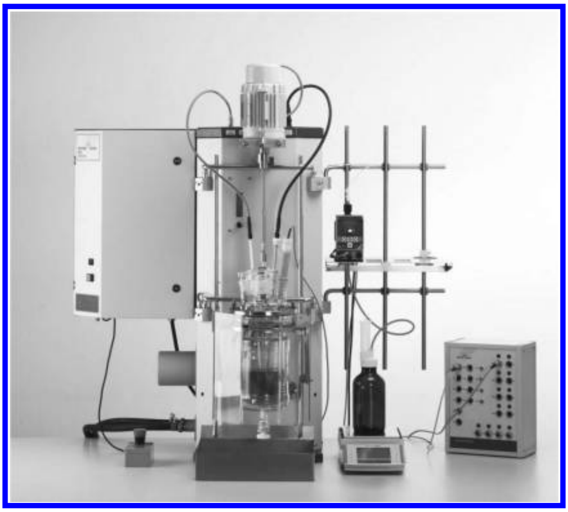
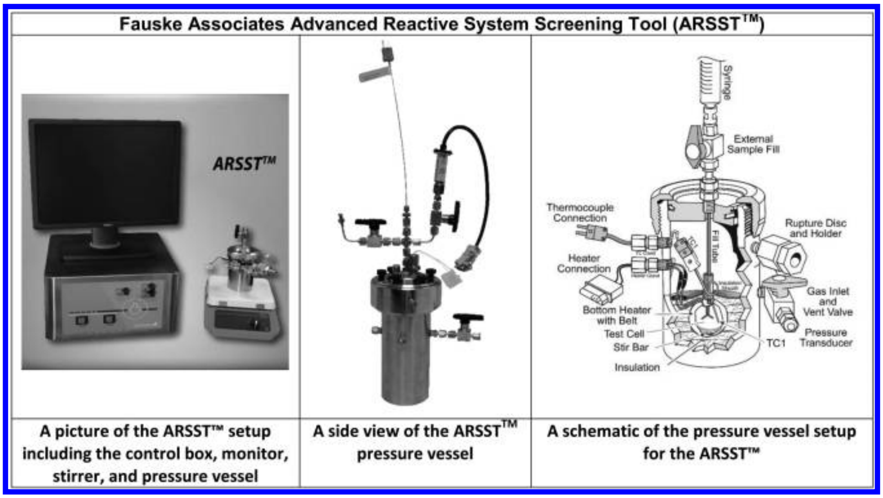


Figure 13. Mettler-Toledo RC1 calorimeter. Photo used with permission of Mettler-Toledo AutoChem, Inc.-www.mt.com/autochem

Measurement or calculation of the adiabatic temperature rise allows prediction of the highest temperature a reaction mixture can attain, at least regarding the planned and desired chemical conversions, which is controlled by the quantities of reagents that are added and that react. It allows determination of some measure of intrinsic safety if, for example, the adiabatic temperature rise is of little consequence and is insufficient to boil off the reaction solvent. Of course a critical aspect is to also confirm that no *unwanted* and possibly more exothermic alternative reaction pathways can be accessed by the worst case adiabatic temperature rise (with a significant safety margin to accommodate risks of localized over-heating as a result of poor mixing efficiency on scale up).

In many nitration reactions for example (*19*), because of the thermal instability of nitrated products, it is generally critical to ensure a high degree of control over the addition of the nitrating reagent (e.g. nitric acid or mixed sulfuric and nitric acids) to ensure full control over the heat of reaction from the desired nitration reaction. It is important in such reactions to control the conversion and heat evolution from the desired nitration reaction. It is also important to ensure that the products of nitration reactions are not allowed to reach temperatures sufficient to initiate decomposition which can lead to explosion due to decomposition exotherms and hence self-heating and accelerating temperature rise as well as pressures generated from gaseous by-products from such decompositions once they occur. A further concern is to avoid elevated temperatures that can cause over-nitration generating even more unstable products and their exothermic decompositions. In such cases, it is also critical for scale-up-safety to determine the onset-temperature, the energy released and the rate of release of gaseous by-products evolved from potential exothermic decomposition reactions, evaluated at different timepoints through the course of reaction and under stressed conditions such as higher reaction temperatures to emulate and avoid potential worst case scenarios (*cf.* discussion of salicylic acid nitration in Scheme 1).

Small scale calorimetry with controlled heating is typically employed to address such concerns, *e.g.* using equipment such as the Fauske Associates ARSST™ (Advanced Reactive System Screening Tool™, Figure 14). This instrument applies a pre-calibrated linear heating temperature ramp to a small sample of the compound or reaction mixture under investigation, which is surrounded by thermal insulation within a pressurized autoclave. The sample temperature is monitored to detect when it exceeds the applied temperature ramp, indicative of a reaction exotherm whose rate and magnitude of increase are used to determine thermal runaway. Pressure is used to suppress solvent evaporation so that temperatures above the solvent boiling point can be evaluated without distortion of reaction heat by latent heat of solvent evaporation. Evolution of heat and generation of additional pressure (beyond the applied pressure) are monitored and quantified to determine both the onset-temperature for thermal and pressure runaway events and also how extreme the energy and pressure release is from any such thermal runaway reaction. This affords an understanding of any danger point towards which it is unsafe for a reaction mixture to be heated.



A picture of the ARSST™ setup including the control box, monitor, stirrer, and pressure vessel

A side view of the ARSST™ pressure vessel

A schematic of the pressure vessel setup for the ARSST™

Figure 14. Fauske Associates ARSST™. Images provided courtesy of Fauske & Associates, LLC

A common misconception is that a safety margin of 50 °C (the so called "50 degree rule") is sufficient between planned reaction temperature and onset-temperature for a thermal runaway measured by DSC or ARSST but this can seriously underestimate scale up safety requirements for a variety of reasons:

1. Both heat transfer and mixing are less efficient at large scale these can result in localized temperature excursions, for example in the vicinity of reactive reagent addition, that exceed the controlled temperature for the bulk reaction mixture. It is accordingly appropriate to include a significant temperature safety margin of around 100 °C (or more, depending on circumstances) between the planned operating temperature for a reaction and the onset-temperature for thermal runaway.
2. Measuring instruments (such as DSC or ARSST) for detecting the onset-temperature for thermal runaway are insensitive below a threshold level of exotherm before the exotherm can be detected and since such instruments may also "overshoot" the true onset-temperature for thermal runaway if the temperature ramp rate used for thermal stability screening is too fast or if exotherm is slow to initiate (so that by the time exotherm is registered the temperature may be higher than the actual exotherm onset). This combination of minimum detection threshold and temperature ramping overtaking the true thermal runaway onset-temperature means that DSC and ARSST can report a misleading and potentially dangerous higher onset-temperature for a thermal runaway than is really the case, giving rise to a false degree of reassurance.
3. Reagents can continue to react over time and continue to increase reaction mixture temperature after cooling failure beyond the temperature at which reactor cooling failed so that a DSC or ARSST onset-temperature for thermal runaway of say 70 °C may imply danger of runaway at much lower temperature such as say 50 °C if accumulated reagents present in the event of cooling failure at 50 °C can continue to heat the reaction mixture to above 70 °C.

Professor Francis Stoessel accordingly recommends that the thermal runaway onset-temperature used for determining a temperature safety margin from operating temperature should be the isothermal temperature up to which the reaction mixture is stable for 24 h under adiabatic conditions so that even slowly initiating exothermic decomposition pathways or other reactions of accumulated reagents are not overlooked (*20*). This 24 h adiabatic stability temperature threshold can also be extrapolated from DSC scan data (*20*). This is discussed further later on in the chapter.

Individual circumstances concerning significant heat evolution rate and explosion risk associated with both thermal runaway decompositions or desired reactions may necessitate more extreme precautions. These may include a larger temperature safety margin (between reaction temperature and thermal runaway onset-temperature) or an alternative reactor design such as a continuous flow arrangement with small reaction mixture inventory and very efficient heat transfer so as to mitigate both the likelihood and the consequences, of misadventure.

Professional advice should be sought for definitive risk assessment, as well as safe process or reactor design, for example using the equipment and/or the services of organizations such as Chilworth Technology Inc (www.chilworth.com), Fauske & Associates (www.fauske.com), HEL Group (www.helgroup.com), Mettler Toledo (www.mettlertoledo.com), Swissi Process Safety GmbH (www.swissips.com) or Inburex Consulting GmbH (www.inburex.com). More comprehensive texts on process safety should also be consulted such as Francis Stoessel's Thermal Safety of Chemical Processes, Risk Assessment and Process Design (*20*), Bretherick's Handbook of Reactive Chemical Hazards (*12*), Barton and Rogers' Chemical Reactive Hazards (*21*), and also the process safety issues of the ACS Organic Process Research and Development Journal.

Oxygen Balance for Anticipation of Instability

A helpful indication of which reagents, reaction products or by-products are likely to be prone to energetic decomposition is provided by the oxygen balance in molecules, determined according to Equation 1 below. Oxygen balance is a measure of a molecule's "self-redox" reactivity or the extent to which it has both powerful oxidizing groups and powerful reducing groups in the same molecule such that reaction of the functionality in the molecule with itself will likely release a lot of energy.

$$\text{Oxygen Balance} = -1600 \times [2C + (H/2) - O] / M$$

where **M** is the molecular weight of the molecule under consideration,
C is its number of carbon atoms,
H is its number of hydrogen atoms
and **O** is its number of oxygen atoms.

Equation 1 - Oxygen Balance equation

The equation reports the molar percentage of oxygen excess over reducing atoms (where carbon atoms are assumed to be oxidized to carbon dioxide and hydrogen atoms are assumed to be oxidized to water, hence 2 x C atom count, with 2 O's *per* C in CO_2, and ½ x H atom count, with ½ O *per* H in H_2O). Thus, a single atom of oxygen equates to an oxygen balance of 100 (sometimes expressed as 100%). If there are other oxidizable elements in a material then further terms are added to the oxygen balance equation to reflect the number of atoms of oxygen that are consumed for the highest oxidation state of that oxidizable element, *e.g.* if sulfur is present then add the term "**+ 2S**" within the [] parentheses.

The oxygen balance gives a measure of how completely a molecule can oxidize itself (through combination of oxidizing and reducing functionality) where a combination of an equal balance of oxidizing and reducing functionality (with oxygen balance of around zero) and a high concentration of oxidizing and reducing functionality in a molecule, compared with other atoms, all equates to potentially highly energetic self-reactive decomposition. High explosives, however typically have a positive oxygen balance (with surfeit of oxidizing functionality over reducing functionality to assist rapid decomposition).

Oxygen balance can also be applied to mixtures of materials comprising oxidizing and reducing agents to determine net self-reactivity and instability of a mixture such as gunpowder, which comprises a mixture of the oxidizing agent potassium nitrate along with reducing agents comprising carbon (charcoal) and sulfur. In the case of mixtures of materials, the composite oxygen balance can be calculated using Equation 2 where m_n is the mass and OB_n is the oxygen balance of each of n components in the mixture (excluding components that will not, under conceivable reaction conditions, participate in oxidizing or reducing reactions such as water or phosphoric acid):

$$\text{Oxygen Balance of a mixture} = \frac{\sum_n m_n \,.\, (OB)_n}{\sum_n m_n}$$

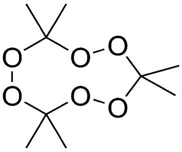
Equation 2 – Oxygen Balance equation for a mixture of components

Materials with an oxygen balance ranging from around minus 200% to plus 100% are potentially likely to demonstrate explosive instability.

Let's look at an example of oxygen balance to predict thermal instability with the case of Richard Reid, the hapless "shoe bomber", who was caught and restrained by flight crew and fellow passengers on the 22nd December 2001 American Airlines flight 63 from Paris to Miami as he tried unsuccessfully to detonate TCAP and PETN explosives packed into the heels of his shoes (Figure 15). TCAP is so-called "tricyclicacetone peroxide" $C_9H_{18}O_6$ (Figure 16) and PETN is pentaerythritol tetranitrate $C_5H_8N_4O_{12}$ (Figure 17).

Published in the FBI Laboratory 2004 annual report
http://www.fbi.gov/news/stories/2005/july/shoe_bomb071805,
FBI Laboratory

Figure 15. One of Richard Reid's explosive shoes



$C_9H_{18}O_6$

Figure 16. TCAP

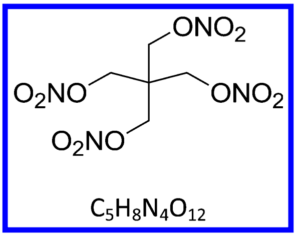


Figure 17. PETN

The oxygen balance for TCAP is calculated as - 1600 x [2 x 9 + 18/2 – 6] / 222 = - 151%

The oxygen balance for PETN is calculated as - 1600 x [2 x 5 + 8/2 – 12] / 316 = - 10%

Thus both of these materials are identified as likely explosives by the oxygen balance alert range of minus 200% to plus 100%.

An even more extreme example is provided by the high explosive glyceryl trinitrite (commonly known as nitroglycerine) whose molecular formula is $C_3H_5N_3O_9$ and for which the oxygen balance is calculated as - 1600 x [2 x 3 + 5/2 -9] / 227 = + 3.5% whilst the oxygen balance for TNT is -1600 x [14 + 2.5 – 6]/227 = - 74%

Of course auto-redox is not the only criterion for instability. For example, lead azide, mercury fulminate and diazonium salts are all prone to explosive decomposition, not through auto-redox chemistry but as a result of exothermic decomposition driven by thermodynamically favorable release of large volumes of energetically stable nitrogen gas at a rapid and accelerating rate. Nitrogen trihalides, generated from reaction of ammonia with halogens can also be a hazard. These also don't contain oxygen atoms but are nevertheless explosive due to energetic decomposition, with rapid release of nitrogen and halogen gases (*e.g.* Equation 3). As a result, it is important to be alert to this risk and to avoid inadvertent exposure of ammonia (and other amines) to halogens or halogen generating materials such as bleach, even in process waste streams.

$$8\ NI_3{\bullet}NH_3 \rightarrow 5\ N_2 + 6\ NH_4I + 9\ I_2$$

Equation 3 – Nitrogen tri-iodide decomposition

Oxygen balance, in combination with critical thinking, can also identify a potential hazard from combination of process waste streams containing methanol with those containing bleach, especially under acidic conditions since this can give rise to methylhypochlorite (MeOCl) (Equation 4).

$$MeOH + HOCl \rightarrow MeOCl + H_2O$$

Equation 4 – Reaction of methanol with bleach under acidic conditions

The oxygen balance equation for methylhypochlorite confirms its instability: -1600 x [2 x 1 + 3/2 – 1] / 66.5 = -60. It is also particularly hazardous due to its low boiling point of 12 °C which means it can give rise to explosive vapors distilling off from process waste streams.

This further illustrates the importance of considering not only the required reaction but also potential unwanted reactions, including the fate and potentially adverse combinations of process waste streams. Bretherick's Handbook (*12*) is again an invaluable guide to anticipate such issues and concerns, such as in this case to recognize the potential hazards from combination of methanol and bleach.

Energetic Functional Groups Requiring Especially Detailed Risk Analysis and Safety Controls

Diligent risk analysis is required for all intended and potentially unintended reactions by consideration of heats of formation and/or decomposition to identify potentially unstable energetic functionalities. Particular attention and concern should be given to intrinsically energetic functional groups as well as energetic combinations of chemicals (whether redox combinations or acid and base combinations). Energetic and relatively unstable functional group classes include acetylenes, oximes & diazonium salts (whose decomposition energies can be around 150 kJ/mol in magnitude), nitroso compounds & azides (with decomposition energies of magnitude around 200 kJ/mol), molecules with peroxide functionality (having decomposition energies of magnitude around 250 kJ/mol) and nitro-organic materials (having decomposition energies of around 400 kJ/mol). Sulfoxides, sulfonyl chlorides, isocyanates, alkenes, hydrazines, epoxides and *N*-oxides can also demonstrate instability although their energies of decomposition are typically lower (around 50 to 100 kJ/mol). Beware too of potential hazards with perchlorates, chlorates, hypochlorites, peroxides, ozonides, diazomethane and highly strained rings.

The stability of specific known materials and material combinations should be checked by reviewing past incident history through literature searching, including consultation of Bretherick's Handbook (*12*). If a potentially unstable chemical functionality is present or if you can foresee any energetic or gas generating decomposition potential through intramolecular or intermolecular reaction, then the materials should be checked by DSC (to assess stability of individual materials as a function of temperature) and by use of ARSST (to assess stability of individual materials as well as reaction mixtures as a function of temperature).

Of course, heats of reaction and heats of decomposition are a measure of thermodynamic potential energy if and when reactions or decompositions occur, whereas in practice there are generally also kinetic influences that may prevent or delay reaction initiation. For example, paper in air is metastable, only browning over decades unless heated above the initiation temperature for oxidative decomposition, popularized by Ray Bradbury in his eponymous novel "Farenheit 451", at which point it will then burst into flames. Similarly, other materials may demonstrate lessening of kinetic barrier activation energy for decomposition in the presence of light, free radicals, friction or shock (such as lead azide used in percussion caps for firearms whose exothermic and explosive decomposition is initiated by hammer shock). Additionally, the decomposition of hydroxylamine, other oximes and peroxides can be initiated by exposure to transition metals such as iron or free radical initiators. Thorough literature searching and measurement of stability (with temperature, shock, radicals, light and other stresses) will help to identify potential problems.

Exothermic Reaction Measurement and Control of Exothermic Reaction Risks

If potential instability is identified for starting materials or products of a reaction or if ***any*** temperature rise is detected at small laboratory scale, then it is critical to ensure that the process can be controlled sufficiently on scale up. This will help to avoid temperature excursions that could attain the uncontrolled degradation onset-temperature within a localized environment. It will also help to maintain a sufficient safety margin between specified process conditions and the onset-temperature for dangerous situations. As previously discussed, a useful expedient is to calculate the worst case adiabatic temperature rise, wherein all materials react and no heat whatsoever is removed but instead serves only to heat and potentially boil the reaction solvent. This then allows the determination of maximum reagent aliquot size that can be added at any one time to ensure that the worst case temperature rise still leaves sufficient safety margin before thermal runaway, whilst also taking into account any solvent loss through boiling that could concentrate and further accelerate reaction rate and heat generation.

The CHETAH® software application (*22*) is an additional useful tool for evaluation of reactions and their components to identify situations where significant heats of reaction and instability may occur (provided appropriate reaction pathways are correctly identified, both for required reaction outcomes as well as potentially unwanted but nevertheless still accessible reactions). The CHETAH® software relies on Benson Group Increment Theory (*23*) to combine calculated and experimentally determined heats of formation for different functional groups. This data is used to predict heats of reaction, heats of combustion, equilibrium constants and other thermodynamic properties of target molecules to help predict instability, explosivity and flammability. Most of the Benson Group data available within the software are however based on gas phase measurement. This is a reasonable approximation for solution phase reactions provided all materials stay in the solution phase, such that heats of solvation for starting materials are approximately equal to and hence cancel out the heats of solvation for products (*i.e.* provided solvation is not very different for products compared with starting materials). Correction factors are needed however if, for example, gases are evolved or solids are precipitated out of solution (negating heat of solvation on one side of a reaction equation but not the other) or if starting materials and products have significantly different heats of solvation (*e.g.* if a highly solvated polar salt is generated from reaction of two relatively non-polar reagents).

For example, if thionyl chloride is reacted with stoichiometric water vapor to cause complete hydrolysis but with no further water to solvate the products, so that gaseous sulfur dioxide and gaseous hydrogen chloride are generated, then the reaction is endothermic:

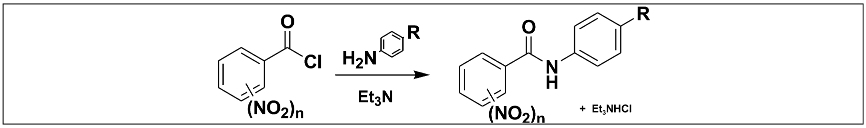
$$\mathrm{SOCl_2 + H_2O \rightarrow SO_2\,(g) + 2\,HCl\,(g)}\quad \Delta H = +50\ \mathrm{kJ/mol}\ \textit{(endothermic)}$$

However if the same reaction is conducted in water as solvent then significant additional energy is released through solvation of the HCl and sulfur dioxide reaction products and the overall heat of reaction becomes significantly exothermic:

$$\mathrm{SOCl_2 + (excess)\ H_2O \rightarrow SO_2\,(aqueous) + 2\,HCl\,(aqueous)}\quad \Delta H = -126\ \mathrm{kJ/mol}\ \textit{(exothermic)}$$

As illustrated by the example above, CHETAH® data and conclusions should be used with caution (especially where assumption of gas phase data would not apply equally to left and right side of reaction equation). CHETAH® should therefore be used primarily as an alerting tool to flag the need for actual experimental calorimetry measurement.

Let us consider a fictitious example comprising reaction of a multi-nitrated benzoyl chloride with a functionalized aniline to give the corresponding amide (Scheme 7) in the presence of one equivalent of triethylamine with 20 parts by volume of cyclopentylmethylether (CPME, bp 106 °C) (*24*) as solvent. Since *ortho*-nitro benzoyl chlorides are known to be thermally unstable (presumably due to intramolecular decomposition reaction, let us also assume that the relevant (fictitious) ARSST and DSC data (with calorimetric tracking of exotherm as temperature is slowly increased) shows the onset of an energetic thermal runaway at 110 °C. Thus, in this case, it would be sensible to impose say a 100 °C safety margin (*33*) between thermal runaway onset-temperature and planned reaction temperature.



Scheme 7. Amide synthesis from nitrosubstituted benzoyl chloride plus substituted aniline

Recall that if a thermal runaway onset-temperature is detected by DSC or ARSST during screening studies deploying a relatively fast temperature ramp rate (~ 2-4 °C per minute), it is generally sensible to repeat the measurement with a much slower temperature ramp rate. This is because if, for example, a runaway onset-temperature of 110 °C is determined with a temperature ramp rate of ~ 4 °C /min, it is likely that the temperature ramp provided by the instrument will have risen above the thermal runaway onset-temperature by the time the runaway is detected by the calorimetric instrument. Hence, once a thermal runaway event has been detected, it is good practice to repeat the thermal runaway determination at much slower temperature ramp rates of ≤ 1 °C /min. The temperature ramp rate should continue to be reduced until the onset-temperature recorded for thermal runaway remains constant between runs. Thus a slower temperature ramp rate might show that the thermal runaway onset-temperature of 110 °C determined with a high temperature ramp rate might actually occur at only 90 °C with a slower temperature ramp rate. In this manner, a more accurate limiting temperature is determined with a minimum of experiments run.

We'll assume for our amide formation reaction, a target reaction temperature of 0 °C, with the benzoyl chloride added to the reaction mixture sufficiently slowly as to ensure that the maximum safe reaction temperature of 10 °C is never exceeded. This results in a 100 °C safety margin before the thermal runaway onset-temperature (determined by ARSST) at 110 °C, where thermal runaway corresponds to exothermic decomposition of the nitrated substrate rather than any desired reaction pathway. The wide temperature safety margin is prudent, both due to onset measurement instrument insensitivity and to ensure that any localized higher temperature regions (where benzoyl chloride is added and where its short-range concentration is momentarily high before it is mixed well into the bulk reaction mixture) do not approach the thermal runaway onset-temperature, even though the bulk reaction mixture temperature may be measured to be well below the runaway onset-temperature. Stoessel also recommends confirming that reaction mixtures are stable for 24 h without runaway at the hottest temperature achievable under adiabatic conditions (see below for further discussion) (*20*).

There is also the need to confirm from lab work that there is no induction period. We wish to ascertain that reaction (and its associated exotherm) ensues immediately upon benzoyl chloride addition without accumulation of unreacted benzoyl chloride so that the progress of the exothermic reaction is therefore indeed fully controlled by the rate of addition of the benzoyl chloride reagent.

Review of predicted heat of reaction data from the CHETAH software along with published thermodynamic data allows estimation of the heat of reaction to be -200 kJ/mol. It should be noted that the major contributor to the overall heat of reaction arises from the acid-base neutralization of the HCl reaction by-product with triethylamine to generate triethylammonium chloride. Furthermore, one must keep in mind that the gas phase data overlooks the significantly greater heat of solvation for the triethylammonium chloride product compared with solvation of all other reaction components. This needs to be corrected by analogy with literature data for similar reactions or by calorimetric measurement.

The heat of reaction can then be applied to the heat capacity of the solvent (since this is by far the major component of the reaction mixture) to determine the worst case adiabatic temperature rise if the acid chloride is to be added in a single portion and without any cooling contribution from the reactor heating/cooling system (*i.e.* "all-in" reagent addition under adiabatic conditions). The heat capacity of CPME solvent is 1.82 kJ/kg.K, thus the adiabatic temperature rise for "all in" addition of the acid chloride to the reaction mixture with 20 parts volume of solvent (density 0.86 g/mL) is calculated as follows:

> Assume a 1 mol scale of reaction to give around 0.430 kg of product (the weight is approximate because the molecular structure and molecular weight are not precisely defined), with 20 parts of CPME solvent.
> This equates to 20 x 0.430 kg = 8.6 L of solvent = circa 7.4 kg of solvent.
>
> With the heat of reaction for the "all-in" addition of 1 mol of benzoyl chloride estimated at -200 kJ, the adiabatic temperature rise is

{200 kJ / 1.84 kJ/kg.K} = 109 °C for 1 kg of solvent
but with 7.4 kg of solvent the adiabatic temperature rise is 109 / 7.4 = 15 °C.

In practice, reactor cooling will be applied and the benzoyl chloride will be added at such a rate that the reaction mixture temperature is maintained at around 0 °C and always below 10 °C. The adiabatic temperature rise calculation is an important measure of intrinsic safety. In this case it demonstrates that even the worst case scenario for this reaction of total cooling failure and a single rapid addition of the benzoyl chloride would still only give rise to an adiabatic temperature rise of ~15 °C (which would only heat the reaction mixture to the initial reaction temperature of 0 °C + 15 °C = 15 °C) which is still well below both the thermal runaway onset-temperature *and* the boiling temperature of the solvent so that reactor pressurization through uncontrolled boiling is also not a concern (although were any solvent to boil, for example with a lower boiling solvent, that too would help to further cool the reaction mixture due to the latent heat of vaporization of the solvent).

A safe procedure for this reaction would therefore comprise slow controlled addition of the benzoyl chloride at a rate balanced to the ability of the reactor cooling system to extract heat from the reactor such that the reaction mixture bulk temperature can be maintained between 0 °C and 10 °C. Intrinsic safety is substantiated by the calculation above showing that even the worst case scenario of cooling system failure and inadvertent dumping in one portion would still equate to a safe outcome. This would also need to be confirmed by DSC or ARSST testing of the reaction mixture at the hottest temperature achievable under adiabatic conditions to confirm stability for a protracted period, ideally 24 h.

Grignard Scale Up Safety Example Illustrating the Need for Reaction Control with Exothermic Chemistry

A further example is provided by synthesis of the breast cancer treatment drug Tamoxifen (Figure 18).

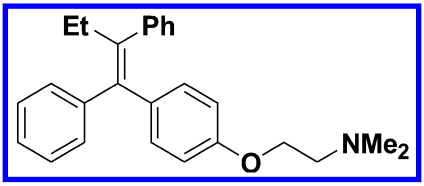


Figure 18. Tamoxifen

A majority of breast cancers are estrogen receptor positive (ER+) which is to say the cancer cells are stimulated to multiply by the natural female hormone estrogen (Estradiol, Figure 19). Tamoxifen is used to treat these cancers as it is metabolized in the liver to Hydroxytamoxifen (Figure 20), which binds to estrogen receptors and blocks the action of estrogen in stimulating cancer cell multiplication in the breast tissue.

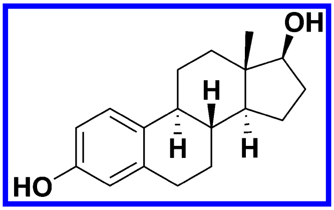


Figure 19. Estradiol

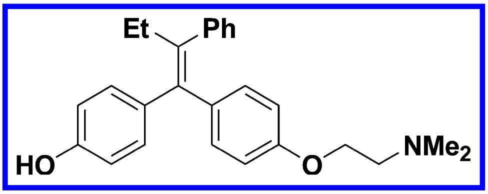
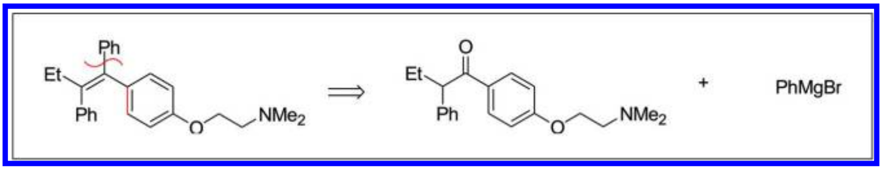


Figure 20. Hydroxytamoxifen

Retrosynthetic analysis of the Tamoxifen molecule suggests a route of synthesis by reaction of the Grignard reagent phenylmagnesium bromide with a corresponding ketone precursor (Scheme 8).



Scheme 8. First step retrosynthetic analysis of Tamoxifen

Let us consider then the industrial preparation of the Grignard reagent by reaction of magnesium metal with phenylbromide (Scheme 9).

$$\mathrm{PhBr} + \mathrm{Mg} \rightarrow \mathrm{PhMgBr}$$

Scheme 9. Phenylmagnesium bromide Grignard reagent preparation

A small-scale (*circa* 50 mL) laboratory research approach to preparation of a Grignard reagent (before such pre-prepared materials were conveniently commercially available) would typically involve adding a full stoichiometric quantity of the bromobenzene to the magnesium metal in diethyl ether or THF and waiting for reaction initiation. Grignard reagent preparation is generally inhibited by a coating of magnesium oxide on the magnesium metal which passivates its surface. A typical laboratory scale technique to overcome this surface passivation is to scratch the surface of the magnesium in the reaction mixture using a glass rod to expose the reactive magnesium metal by mechanically disrupting the oxide coating at the surface. This would generally be done whilst also warming the round-bottomed-flask reaction vessel with a heat source, such as a hot air gun, to stimulate reaction, albeit with an ice bath close at hand in case of overly rapid reaction and solvent boiling. Other techniques for initiation of Grignard reagent formation include addition of elemental iodine crystals and/or a small amount of reactive 1,2-dibromoethane (which decomposes to ethylene gas on Grignard reagent formation) or adding DIBAL, or even adding preformed target Grignard reagent.

Once reactivity is achieved on the surface of the magnesium metal, the Grignard formation then typically proceeds with *gusto* since Grignard initiation is effectively autocatalytic once reaction occurs as any Grignard reagent that is formed then helps to disrupt the remaining oxide coating elsewhere on the metal. A potential complication though, if equipment and materials (especially hygroscopic solvents) are not rigorously free of moisture, is that initial Grignard formation is quenched by residual water content and overall initiation is inhibited until all residual moisture has been consumed.

Once any moisture is quenched and magnesium is sustainably activated, the sustained onset of Grignard reagent formation is then readily apparent thanks to the exothermicity of the reaction, with heat of reaction typically greater in magnitude than -200 kJ/mol. This causes a rapid temperature rise and effervescence from reaction mixture solvent boiling which can be moderated at lab scale by using an ice bath to cool the reaction flask. This sort of procedure, whilst effective at small lab scale, would be catastrophic at large scale where the induction period before Grignard formation initiation introduces the risk of accumulating a potentially dangerous quantity of the unreacted bromo-reagent (assuming addition of bromo-reagent to magnesium and if addition of that reagent to the reaction mixture gets ahead of reaction progress such that the accumulated reagent can suddenly proceed to react after the initiation delay). The autocatalytic nature of the reaction, whereby any Grignard reagent formed serves to increase the reactive magnesium surface area for reaction with the accumulated bromo-reagent, combined with the rapidly accelerating reaction rate with increasing temperature (reflected by the Arrhenius equation) and the decreased heat transfer efficiency at large scale, compared with lab scale, all result in rapidly accelerating reaction rate, heat evolution, solvent evaporation rate, pressurization and risk of sudden expansion and possibly explosion.

The consequences of overheating and an accelerating reaction rate may be less serious for this type of reaction at small lab scale. The accelerating heat of reaction at small scale can generally be accommodated by the rate of distillation of the reaction solvent increasing as latent heat of evaporation of solvent serves to absorb the heat of reaction. This, combined with the large condenser bore (large cross sectional area of small scale lab equipment relative to the volume of solvent vapor produced), means that vapor can be disengaged and escape faster than it is produced. At large scale, however, the rate of vapor generation is more likely to exceed the rate that the vapor can escape due to smaller cross sectional area of vapor uplift piping relative to volume of gas produced, compared with lab scale, leading to risks of reactor pressurization and explosion on scale up, along with "all in" reactive reagent addition precluding subsequent reaction control (even with slow reagent addition, since the induction period before reaction initiation with magnesium can nevertheless result in reagent accumulation).

For safe scale up of Grignard reagent preparation, as with any other reaction, it is important to ensure either that one is always in full control of the heat of reaction or that the heat of reaction is inconsequential. Recognizing that the simplest control to engineer is by controlling the addition of the bromo-reagent (as it is easier to control addition of liquids to a reactor than to control addition of solid magnesium in the case of the Grignard reagent formation) one should ensure that there is never much more bromo-reagent added than the amount whose heat of reaction can be safely accommodated with adiabatic temperature rise, notwithstanding reactor heat transfer capabilities. Thus, in this case, it is most appropriate at large scale to add the bromo-reagent in small aliquots, with aliquot size chosen to ensure that the exotherm caused by addition of each aliquot is insufficient to heat the reaction mixture to the boiling temperature of the solvent (or anywhere near any thermal runaway temperatures measured by DSC or ARSST) under the worst case scenario of adiabatic conditions, where it assumed that heat may be generated so quickly that no heat whatsoever is removed through the reactor jacket or where reactor cooling has failed.

This can be exemplified with a Grignard reagent preparation in a 10,000 L reactor containing 100 kg-mol (*25*) of THF solvent (with boiling point = 66 °C), stirred with 5 kg-mol of magnesium metal granules at 20 °C. Assuming a heat of reaction of -250 kJ/mol for the Grignard preparation and a heat capacity for the solvent of 125 J/(mol.K), addition of the full 5 kg-mol amount of the bromo-reagent to the stirred mixture of magnesium and solvent would release 5,000 mol x 250,000 J/mol = 1,250,000,000 J of energy upon reaction. With the 100 kg-mol of solvent indicated above, this amount of energy released under adiabatic conditions (assuming no solvent vaporization from the reaction mass) would heat the solvent by 1,250,000,000 / (125 * 100,000) = 100 °C. This would likely be dangerous as the 100 °C temperature rise, from a starting temperature of 20 °C, would exceed the 66 °C boiling temperature of the THF solvent and would cause rapid vaporization of a portion of the solvent. Hence the bromo-reagent would need to be added in aliquots of around 1/10th of the total stoichiometric amount (equating to a 10 °C adiabatic temperature rise) to ensure that the worst case adiabatic temperature rise does not remotely approach the boiling temperature of the solvent (even at the localized region of bromo-reagent addition).

A good safety margin between the maximum process temperature and the boiling point of the solvent is necessary. This is to compensate for deteriorating mixing efficiency on scale up that would otherwise result in a larger localized temperature rise and potential for rapid gas liberation through solvent boiling around the vicinity of the bromo-reagent addition zone, if it reacts rapidly on addition before it has mixed in to the reaction mixture as a whole.

As described above, another safety challenge on scale up of the Grignard formation is due to the induction period for magnesium activation while waiting for erosion of the passivating oxide coating on the magnesium. This means that if no reaction occurs with the first aliquot, representing 1/10th of the stoichiometric charge of bromo-reagent, and then subsequent aliquots are added before the prior aliquot(s) react, there is again the opportunity for a dangerous release of energy when reaction does finally get underway. Hence for exothermic reactions with an induction period, it is important to seek evidence of substantive prior aliquot reaction before the next aliquot is added. With an exothermic reaction, a reaction mixture temperature log, for example with reactor cooling temporarily suspended for each aliquot, would provide very clear evidence of when reaction is initiated by means of a temperature kick and, if the appropriate calculations are done to integrate heat flow, then the degree of reaction can also be determined.

In order to prevent reagent accumulation and uncontrolled reaction (after delayed initiation), it is important to write batch instructions to preclude further addition until the temperature rise spike is seen and completed for the previous aliquot. Sampling and analysis of the reaction mixture by quenching into an electrophile can also allow quantitative analysis of the extent to which initiation has occurred after a previous aliquot has reacted. In any event, it is important to ensure (whether by reaction mixture analysis or by temperature monitoring, Process Analytical Technology, or other means) that each aliquot has reacted before the next is added. The same principle applies if exothermically reactive reagents are added continuously to a batch reactor, rather than portionwise (by aliquots) as it is again important to ensure that addition rate does not get too far ahead of reaction rate so as to avoid a dangerous quantity of reactive reagent accumulating and then giving rise to uncontrolled temperature excursion and potential for thermal runaway.

Again as mentioned above, a further danger with the Grignard reagent preparation is associated with the potential for contamination of reaction equipment or solvent by water. Since water has such a low molecular weight, small amounts of water can represent significant molar quantities, especially compared with portionwise aliquots of small quantities of reagent. Thus if a 1/10th stoichiometric quantity of bromo-reagent is added during the Grignard preparation in the 10,000 L reactor example above, then just a few kg of water in the thousands of kg of reaction solvent (representing < 0.1% water content in the solvent) would be sufficient to completely quench the full first aliquot Grignard reagent preparation and prevent magnesium activation. This introduces the temptation to add subsequent aliquots through frustration or desperation to drive reaction initiation, with the risk again of thermal runaway once the inhibiting water content is consumed and the accumulation of subsequent aliquots finally undergo reaction initiation, with a significant accumulation of reagents present and consequent uncontrolled temperature excursion beyond reactor cooling capabilities.

Finally, a further influence over the rate of Grignard preparation reaction progress (and hence the rate of heat generation) is of course also the total surface area of the magnesium. The surface area available for reaction is dictated by the particle size distribution. A smaller particle size distribution equates to a larger total surface area for a given quantity of magnesium. As explained above, the induction period before reaction initiation is usually limited by the extent of the oxide coating on the surface of the magnesium. It is essential therefore that laboratory work should be done to define safely scaleable process technology with representative samples of the reagents to be used for large scale production, ideally taken from the same lots of material and solvents (though with diligent measures deployed to exclude air and moisture during sampling of the material to prevent degradation through further surface oxide coating). Labwork done with new lots of large magnesium granules could prove misleading in terms of induction delay, ease of initiation and rate of heat generation. If an older, finer powder form of magnesium is used instead for large scale production, this powder could demonstrate slower induction due to a more substantial oxide coating and then much more rapid heat generation once reaction gets under way than would be the case with larger, freshly supplied granules.

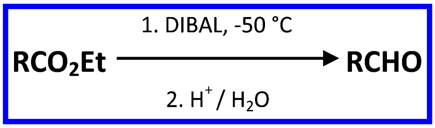
As well as the need for process chemistry to be proved with raw materials representative of those to be used for large scale, a scale up factor much greater than 10, from one scale to the next, should ideally be avoided to prevent significant surprises due to differences in mass transfer or heat transfer efficiency on scale up. Furthermore, reactions for scale up should ideally be modeled with reaction equipment closely emulating reactor geometry design for large scale (with parallel sided reaction vessels having flanged joints, jacket heating and cooling and with agitator design and agitator speed approximately representative of large scale operation, ideally no smaller than 2 L in volume and with reactor preparation, cleaning and drying procedures representative of plant operation, to best model larger scale process operation, with no surprises on scale up from, for example, cleaning solvent residues).

Returning to the Tamoxifen synthesis (Scheme 8), once the Grignard reagent is prepared by aryl halide metallation with magnesium, the subsequent steps of Grignard addition to the ketone and then acid workup are much more easily controlled by means of controlled addition of the Grignard solution to the ketone, followed by controlled addition of the product reaction mixture to the acid workup for Grignard quench and heating to eliminate water to prepare the Tamoxifen API. Since the steps of Grignard addition to ketone and Grignard quench are rapid and addition controlled, provided they are not run too cold, there is little danger of reagent accumulation so long as the reactions are conducted with slow additions and addition rates are designed to match the heat transfer capabilities of the cooling system to extract heat during each of the two operations.

It is important, especially for the typical aqueous acidic work up step, to ensure that good control of heat of reaction is achieved by control of addition rate. Thus it is generally better to transfer the Grignard product reaction mixture at a controlled rate to the aqueous workup mixture so that the heat of reaction of workup is controlled throughout the transfer process. The alternative "inverse" workup approach of adding aqueous workup solution to the reaction mixture means that all the heat of reaction (on quenching the Grignard addition product with water) is generated with addition of just the first small portion of the aqueous workup mixture. Since a full stoichiometric quantity of water will be present with just a small portion of the aqueous workup mixture, it would be much more difficult to control the generation of heat with addition of aqueous workup to the Grignard addition product by this alternative workup approach, compared with the more evenly controlled rate of heat generation with transfer of Grignard addition product to aqueous workup mixture (notwithstanding the heat capacity and cooling capability for the quench solution to which the reaction mixture is added).

DIBAL Workup Example Illustrating the Need To Consider the Fate and Properties of All Reaction Products

It is always important with any chemical reaction to think carefully about all of the reaction steps and the safety implications of each step on scale up. Unwanted reaction pathways can give rise to major hazards, as has been described in some of the earlier examples above (*e.g.* with thermal runaway due to nitroaromatic decomposition and with unintended consequences of water ingress resulting in unstable ketene formation and decomposition). However, some desired reaction pathways may also give rise to unrecognized hazards if not considered carefully. Consider, for example, the reduction of an ester to the corresponding aldehyde using di-*iso*-butylaluminium hydride (DIBAL) (Scheme 10).



$$RCO_2Et \xrightarrow[\text{2. } H^+ / H_2O]{\text{1. DIBAL, -50 °C}} RCHO$$

Scheme 10. Ester reduction to aldehyde using DIBAL

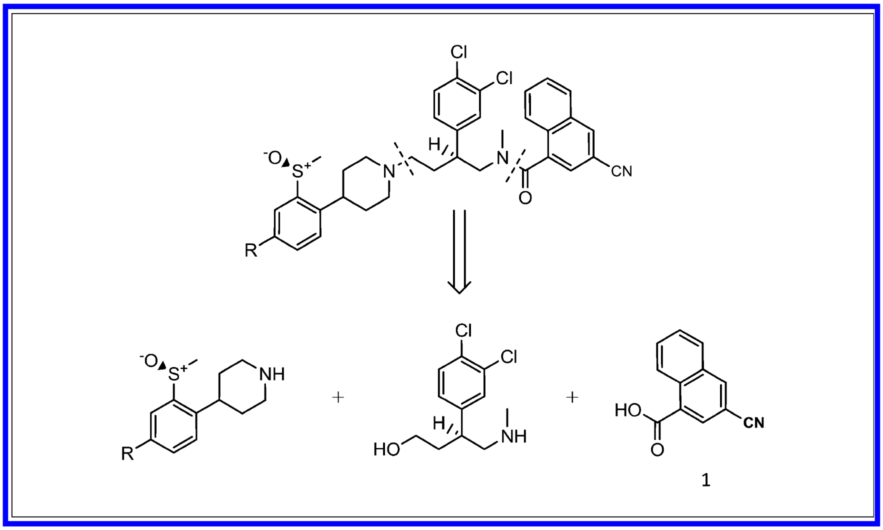
It can be easy to consider the DIBAL simply as a tool that delivers the required reaction outcome, without adequate consideration of the underlying chemistry and potential safety hazards that can arise on scale up. Thus with the DIBAL reduction of the ester, a typical small laboratory scale procedure might involve dropwise addition of 1 M DIBAL to a stirred solution of the ester at -70 °C (with DIBAL chosen over other reducing agents so as to minimize further reduction to the corresponding alcohol due to trapping of the aldehyde intermediate as a hemiacetal aluminum complex). This reaction would typically be followed by a cold quench with methanol to destroy excess unreacted DIBAL (hydride) and would then be treated with aqueous acid to liberate the desired reaction product from aluminum complexation. The reaction mixture is then typically heated to ambient temperature before isolating the aldehyde product by extraction and removal of solvent by evaporation. Whilst this procedure gives little concern at small scale, it can become very hazardous on scale up.

The scale up problem in this case is not so much the heat of reaction of DIBAL with the ester, since the liquid DIBAL solution can be carefully added at a rate which allows the heat of reaction to be removed at a sufficient rate to maintain the low temperature required for reaction selectivity, balanced by the heat transfer capabilities of the reactor cooling system. The potential problem however arises during the acidic aqueous workup which causes hydrolysis of the aluminum-product complex, liberating 2 equivalents of *iso*-butane boiling at -12 °C. Thus, the scale up of this reaction into a 50 L glass reactor (which is unable to withstand more than a few psig of pressure), with about 15 mol of reactant would release 30 mol of *iso*-butane into the reactor free headspace of around 10 L volume.

Heating the post-workup mixture through the -12 °C boiling point of the flammable by-product to ambient temperature therefore results in rapid release of a volume of gas equating to around 650 L at standard temperature and pressure. This would, at best, cause frothing up of the reaction mixture through reactor overhead fittings (due to the decreased surface area of reaction mixture surface *per* volume of gas for gas disengagement, compared with small lab scale). In a worst case scenario, however, it could cause fracture of the glass reaction vessel and the release of flammable gas if the rate of venting from the 10 L reactor headspace cannot keep pace with the rate of gas boil off. The estimated 650 L of gas released into a 10 L headspace without adequate venting could equate to a pressure of up to 1000 psi). Hence in this case it is important to consider and to moderate the rate of heating even after completion of reaction and workup, to ensure a safely dissipated rate of *iso*-butane gas liberation. This example illustrates the need to consider carefully the properties and fate of all reaction by-products and their associated risks.

Synthesis of 3-Cyano-1-naphthalenecarboxylic Acid: An Example That Illustrates the Need To Monitor and Control All Reactive Intermediates

While it was shown that it is important to avoid accumulating unreacted reagents that may react uncontrollably upon initiation, it is similarly important to also ensure that there is no risk of accumulating reactive intermediates. An example of reactive intermediate control is provided by the synthesis of 3-cyano-1-naphthalenecarboxylic acid (Scheme 11), an intermediate for synthesis of a number of neurokinin antagonists that were explored by AstraZeneca as a possible treatment for asthma and other therapies (*26*).



Scheme 11. Retrosynthetic analysis of neurokinin antagonist drug candidates

The structural simplicity of the naphthalene cyano acid belies its synthetic complexity since *meta*-directing (deactivating) substituents **Z** on naphthalene ring 1 direct electrophilic aromatic substitution to the other naphthalene ring 2 rather than to the *meta*-position on ring 1 as desired, whilst activating substituents **X** on ring 1 direct electrophilic aromatic substitution to the *ortho* and *para* positions on ring 1 rather than to the *meta*-position required for synthesis of the cyano acid (1) (Figure 21).

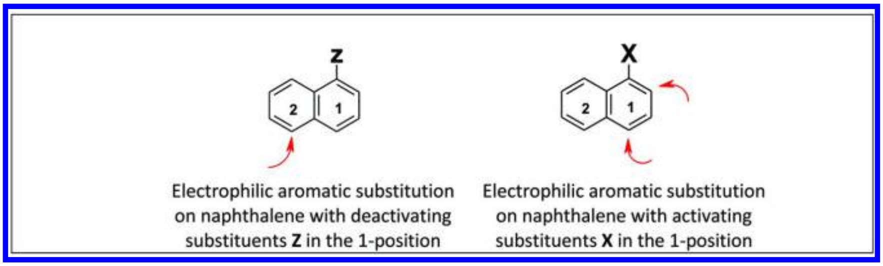
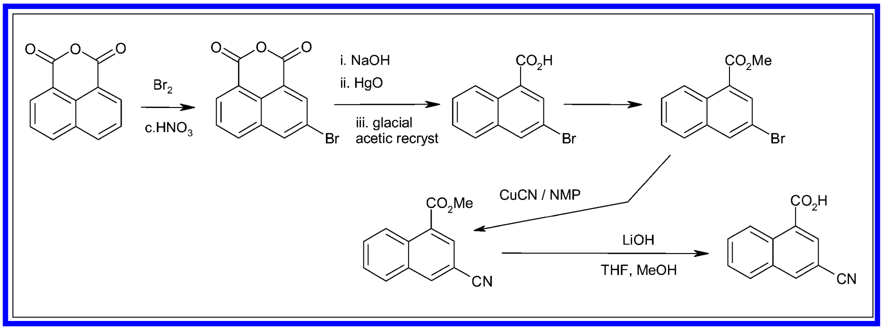


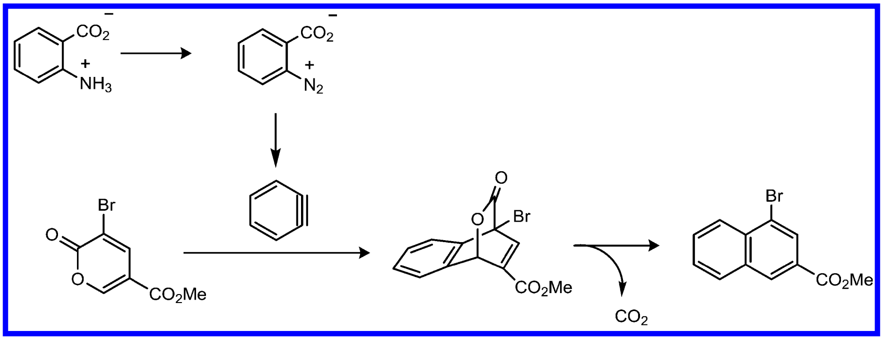
Figure 21. Electrophilic substitution directing effects with 1-substituted naphthalenes

The medicinal chemistry route (Scheme 12) to cyanoacid (**1**) overcame the misdirection to the wrong naphthalene ring with *meta*-directing substituents, by use of symmetrically disubstituted (*meta*-directing) 1,8-naphthalic anhydride followed by selective decarboxylation. This route was effective in supplying material for early drug candidate testing but was inefficient and inappropriate for larger scale manufacture due to low yielding and challenging bromination in a huge excess of nitric acid, followed by stoichiometric use of highly toxic and costly mercuric oxide to effect the selective decarboxylation, as well as toxicity of stoichiometric cyanide and very low overall yield.



Scheme 12. Initial route of synthesis to naphthalene cyanoacid building block

A more efficient and less problematic alternative route was needed to supply the cyanoacid at a larger scale for drug development. After considering a total of over 70 possible alternative route approaches, the preferred route that was selected for development and manufacture (Scheme 13) overcame the problem of 1,3-naphthalene ring substituent orientation by introducing the necessary *meta*-substitution pattern in a preformed bromo-coumalate single ring component. The naphthalene double-ring structure was then constructed by Diels Alder cycloaddition between bromo-coumalate and benzyne (which was generated by *in situ* nitrosation of anthranilic acid to achieve diazotization, followed by decomposition to benzyne through loss of carbon dioxide and nitrogen). The product, after cycloaddition and decarboxylation, was 1-bromo-3-carboxynaphthalene which could then be converted to the required cyanoacid.



Scheme 13. Key steps of preferred route of synthesis for scaled up supply of cyanoacid building block

The route from anthranilic acid to the desired bromonapthalene involves an unstable and potentially explosive diazonium salt, an extremely reactive and potentially hazardous benzyne intermediate, and a gas-generating decarboxylation step which could also give rise to pressurization and explosion risk if not well controlled. Safe scale up of these reaction steps was established by kinetic study of the rate of formation of the bromonaphthalene ester product and associated carbon dioxide gas generation, which were correlated against *iso*-amyl nitrite addition for amine nitrosation at different reaction temperatures. This work allowed definition of a reaction temperature and nitrite addition rate at which the 4 “single pot” concerted reaction steps (of diazonium formation, benzyne formation, cycloaddition and decarboxylation) were are all controlled by rate of addition of isoamyl nitrite, with no accumulation of potentially dangerous diazonium intermediate, benzyne or lactone. This was confirmed by a combination of reaction calorimetry, off-gas (carbon dioxide) volume measurement vs. time, and reaction mixture analysis by HPLC vs. time to demonstrate that all steps could be made to be addition controlled by the rate of addition of nitrite without accumulation of unstable intermediates when the reaction is carried out at the 85 °C boiling temperature of the dimethoxyethane solvent.

9(10H)-Acridinone (Figure 22) was identified as an unwanted by-product generated from competing reaction of benzyne with the anthranilic acid starting material but this by-product formation was mitigated by controlled co-addition of *iso*-amyl nitrite and anthranilic acid through 2 separate addition lines to the reaction vessel so as to minimize the concentration of unreacted anthranilic acid through the course of the reaction and hence to favor the reaction of benzyne with the bromoester diene (bromocoumalate) component of the desired Diels Alder cycloaddition, rather than reaction with unreacted anthranilic acid. The small amount of the 9(10H)-acridinone that was still generated was easily removed by crystallization from the reaction product.

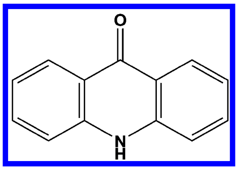
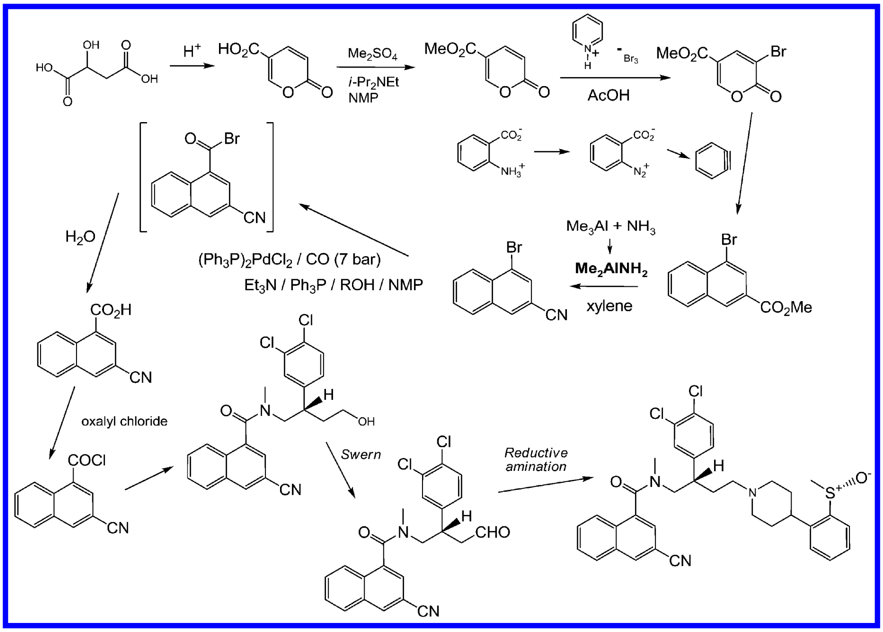


Figure 22. Acridinone by-product

The new route chemistry allowed safe and efficient scale up for neurokinin antagonist synthesis (Scheme 14) in much improved yield and without the safety and mercury contamination concerns associated with the original route of synthesis (*26*).

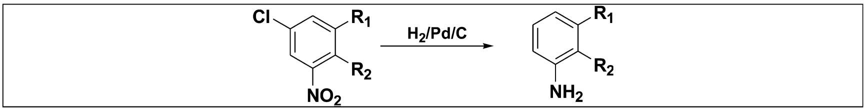


Scheme 14. Overall route of synthesis to cyanoacid and from that to NK antagonist drug candidate

Reduction of Nitro Group via Catalytic Hydrogenation: A Further Example of the Need To Understand and Control Reactive Intermediates

Another example that demonstrates the need to control reactive intermediates is provided by the reduction of a chloronitroaromatic compound by catalytic hydrogenation. This need for control is because nitro reduction introduces the risk of accumulation of unstable and reactive oxime intermediate (potentially arising from hydrogen starvation during hydrogenation of nitroaromatics to anilines). This is in addition to the thermal instability of nitroaromatics (having high energy of decomposition of magnitude around 2000 kJ/mol (*30*)) and the significant exothermicity of the nitro reduction reaction (having heat of reaction of magnitude 560 kJ/mol (*30*)).

Isochem in France needed to hydrogenate a chloronitroaromatic substrate to prepare a corresponding hydrodehalogenated aniline (Scheme 15) (*27*).



Scheme 15. Isochem hydrodehalogenation and nitro reduction

The Isochem scientists were diligent in measuring the heat of their reaction using a reaction calorimeter and in then using that data to estimate the adiabatic temperature rise for the reaction mixture (as a “worst case” determination of the maximum rise in the temperature of the reaction mixture). They specified a reaction temperature of 80 °C, working with ethanol as solvent having boiling temperature around 150 °C at the 10 bar pressure they planned to run the reaction. They furthermore determined that the maximum (adiabatic) temperature rise for their reaction would be 41 °C (for worst case conditions with coolant failure, whereby the entire heat of reaction served to heat the reaction mixture with no heat loss). They also checked the thermal stability of a sample of the reaction mixture at the end of the reaction by using a controlled temperature ramp in a calorimeter (which can be done using DSC or ARSST) and identified an onset-temperature for a thermal runaway at 280 °C by DSC. This appeared to suggest adequate reaction safety for scale up since the highest temperature the reaction mixture could reach in the event of cooling failure would be 80 °C + 41 °C = 121 °C which was 159 °C below the onset-temperature they’d recorded for thermal runaway of 280 °C.

A further safety margin was apparently afforded by the latent heat of evaporation of the ethanol reaction solvent whose boiling temperature (under the planned reaction conditions of 10 bar gauge pressure) of around 150 °C lies between the maximum adiabatic temperature and the thermal runaway onset-temperature, so that any further unanticipated temperature excursion would first of all encounter the solvent boiling temperature. Hence at first sight it appeared that any heat generated could be absorbed by boiling of the solvent at 150 °C before any higher temperature could be accessed (assuming that the increased pressure from boiling of solvent would be vented by the reactor pressure relief system to avoid suppression of solvent boiling by increasing pressure). This therefore appeared to be a safe reaction.

A warning bell was however rung for the Isochem scientists when they inadvertently deployed a 50% reduced charge of catalyst in one of their experiments (through miscalculation of the catalyst quantity necessary for their reduction by omitting to make allowance for the water content of the 50% water wetted catalyst, kept wet to avoid catalyst pyrophoricity, *cf.* operational hazards discussion below). The DSC trace for the reaction mixture after reaction with the halved catalyst charge showed a worryingly lowered thermal runaway onset-temperature of 146 °C and another at 230 °C (Figure 23), both at much lower temperatures than the 280 °C runaway onset-temperature that they'd previously measured with the full catalyst charge! The thermal runaway onset-temperature of 280 °C that they'd measured previously was 200 °C higher than the planned reaction temperature of 80 °C and was above the 150 °C boiling temperature of the solvent under the planned reaction pressure. The newly measured thermal runaway onset-temperature of 146 °C was however only 66 °C hotter than the planned reaction temperature and was *below* the solvent boiling temperature, so that the latent heat of evaporation of the solvent no longer provided a safety buffer for heat absorption to help prevent access to the thermal runaway onset-temperature. Hence the scale up hazards were perceived to have increased, although, as is described below, the actual scale up hazards were not really increased but were simply better recognized by virtue of the half-catalyst-charge experiment.

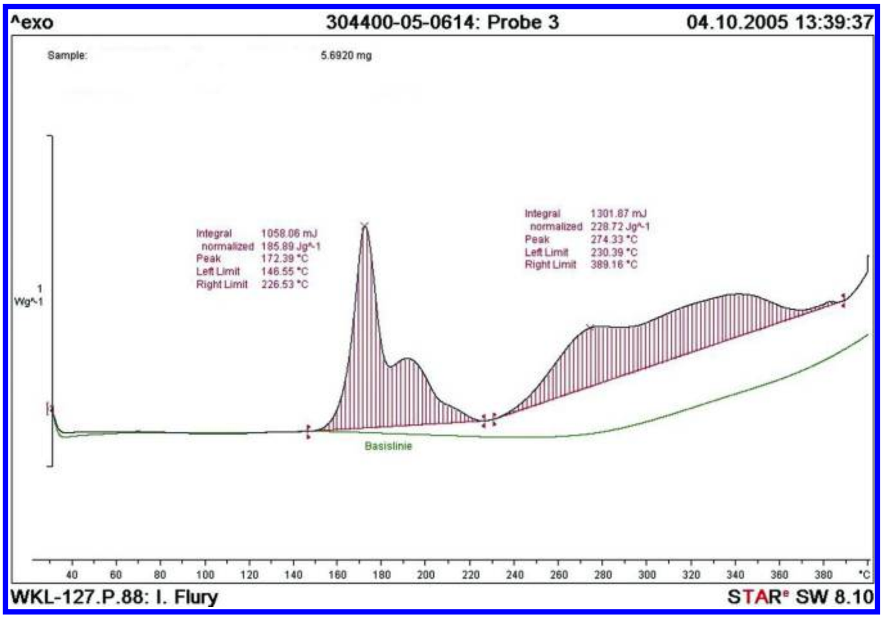


Figure 23. DSC of Isochem incomplete hydrogenation reaction mixture after reaction stalled with half catalyst load

The reduction of a nitroaromatic to an amine by hydrogenation progresses by stepwise introduction of reactive hydrogen atoms in conversion of nitro to nitroso to hydroxylamine to amine, with a total of 3 mol of hydrogen *per* mol of nitroaromatic being required to achieve complete reduction (Scheme 16). This is aside from the additional step of the hydrodechlorination in the Isochem case which also consumes a further equivalent of hydrogen.

$$ArNO_2 + H_2 \rightarrow ArNO + H_2O;\ \ ArNO + H_2 \rightarrow ArNHOH;\ \ ArNHOH + H_2 \rightarrow ArNH_2 + H_2O$$

Scheme 16. Reaction steps for reduction of nitroaromatic to amine

When the Isochem scientists measured the DSC of their reaction mixtures at the end of their hydrogenation reactions with the full catalyst charge they were essentially testing the stability of the hydrogenation reaction product (namely their amine product). When they ran their DSC with the half catalyst charge case, however, their hydrogenation reaction had stalled (indicative of catalyst inactivation by poisoning with the lesser amount of catalyst, presumably due to a small amount of an impurity in sufficient quantity to poison the half catalyst charge but with insufficient quantity to poison the full correct catalyst charge). This stalled hydrogenation with the half catalyst charge presumably caused accumulation of the hydroxylamine intermediate having lesser stability than the final amine product which would explain the lower thermal runaway onset-temperature seen by DSC with the half catalyst charge example.

It is important in undertaking reaction mixture stability testing to ensure that the worst reasonably achievable case is tested. In the Isochem example, since the nitroaromatic starting material and hydroxylamine intermediate are the two likely most unstable species, reaction stability testing should have been carried out with reaction mixtures that were prepared to maximize these two species.

Once alerted to the decreased thermal runaway onset-temperature that occurred with incomplete nitro reduction, Isochem were again diligent in undertaking extensive scale up safety assessment studies both themselves and with involvement of external consultants for pressure calorimetry work. They engineered efficient hydrogen mass transfer on scale up by specifying a hollow-shaft gas-entraining agitator for efficient hydrogen gas dispersion into the reaction mixture and monitored reaction mixture composition and stability by sampling and testing through the course of their hydrogenation reactions during development and scale up of their manufacturing process. They also then implemented close safety-related process parameter monitoring for routine production, tracking hydrogen pressure, hydrogen flow and reaction temperature *vs.* time, with measures in place to flag and respond appropriately to any process deviations. By these means they were able to safely scale up and manufacture their products without incident (*28*).

In the case of nitro reduction and other exothermic hydrogenations carried out under elevated hydrogen pressure, at or above the atmospheric boiling point of the chosen reaction solvent, an additional sensible expedient in the event temperature rises above defined safe control boundaries, *e.g.* due to cooling failure, is to engineer a slow controlled depressurization of reactor headspace to the reactor condenser as a prelude to any emergency pressure relief if control is still not achieved (*29*). Such a controlled depressurization has the advantages of:

(i) decreasing hydrogen concentration so as to attenuate reaction rate (and rate of heat evolution),
(ii) evaporating the reaction solvent which results in heat removal through latent heat of solvent evaporation (ideally with reflux return to avoid substrate concentration and to effect further cooling of the reaction mass by the cooled solvent condensate stream). The result is to cool the reaction mass to the atmospheric boiling point of the solvent and keep the reaction mass in the reactor (as opposed to ejection from the reactor which would occur with emergency pressure relief through a bursting disk or other sudden emergency pressure relief device).

Stoessel has published a very helpful study of nitro group reduction (*30*) detailing successive DSC traces for hydrogenation reaction samples through the course of nitro hydrogenation to amine. This shows increased instability (in terms of lowest thermal runaway onset-temperature) when around 70% of the stoichiometric hydrogen has been consumed, approximately corresponding to maximum accumulation of hydroxylamine intermediate (since 2/3 of the hydrogen usage, approximately 70%, equates to the first two steps of the nitro hydrogenation steps depicted in Scheme 16, assuming the final step of hydroxylamine reduction is the slowest of the three, although in cases where hydroxylamine reduction is fast there is no problem since unstable hydroxylamine won't accumulate, even with hydrogen starvation).

The initial hydrogenation reaction mixture DSC in the Stoessel study, before any hydrogen is consumed, shows the energetic instability of the nitroaromatic starting material with a substantial exotherm corresponding to around 900 kJ/kg, initiating from around 300 °C. As hydrogenation progresses, a new DSC exotherm peak with lower decomposition onset-temperature at around 170 °C (but lesser energy of decomposition of around 150 kJ/kg) is encountered and this latter DSC peak is maximized when around 70% of the full hydrogen uptake is consumed (corresponding to oxime intermediate maximization). Both of the two exotherms in the Stoessel study (commencing at around 170 °C and around 300 °C) are however essentially absent by the time 100% hydrogen uptake is reached (when both the nitro and the hydroxylamine unstable functional groups are fully consumed and converted to the stable final amine product).

Hence the DSC reaction stability investigations for the Isochem reaction should ideally have been run to evaluate reaction mixture stabilities for the potentially worst case conditions comprising:

(i) the start of the hydrogenation (when unstable nitroaromatic content is greatest), and
(ii) the reaction mixture stability at various stages of hydrogen consumption under potential hydrogen starvation conditions (emulating deteriorating

mass transfer of hydrogen gas to reaction mixture on scale up, when unstable oxime intermediate content could be greatest).

Since the relative rates of the various reaction steps in the Isochem example had not been determined, it would have been appropriate to test the reaction mixture for stability using DSC after consumption of 2 and 3 of the 4 molar equivalents of hydrogen needed for nitro reduction and for hydrodechlorination, to ensure that the mixture containing maximum oxime was tested. In the event though, the inadvertent half catalyst example, for which the reduction reaction stalled, was useful for Isochem by providing them with a destabilized reaction mixture containing an increased amount of unstable hydroxylamine reaction intermediate to help them design safer reaction conditions to accommodate the instability of this intermediate.

Scale up of hydrogenations without appropriate reactor engineering design can result in deteriorating mixing efficiency and deteriorating efficiency in mass transfer of hydrogen gas into the liquid reaction mixture due to decreasing surface area available for mass transfer of hydrogen (from gas to solution phase through the top surface of the reaction mixture) relative to volume on scale up. This is aside from the heat transfer requirements to safely dissipate the significant heat of reaction to ensure safe control of temperature through the reaction, with an adequate safety margin before thermal runaway onset-temperature. It is likely with nitro to amine hydrogenations that an inefficiently designed large scale reactor could give rise to greater problems of incomplete reaction and accumulation of unstable hydroxylamine intermediate than would be the case with a small lab scale reactor. Hence the importance of anticipating the impact of reduced hydrogen mass transfer efficiency on reaction mixture stability by conducting experiments to simulate hydrogen starvation. This would allow evaluating the effects on reaction mixture stability from a shortfall of hydrogen gas introduction compared with the stoichiometric requirement, followed by testing of each of these reaction mixtures by DSC and/or ARSST for thermal runaway onset-temperature determination. This then allows appropriate process design to ensure safety, not only for the ideal reaction conditions (where nitro functionality is reduced smoothly to amine without hydroxylamine accumulation) but also for the worst case situation where deteriorating hydrogen mass transfer efficiency on scale up allows accumulation of the less stable hydroxylamine intermediate with consequential decreased thermal runaway onset-temperature. This was encountered fortuitously by the Isochem scientists with their reduced catalyst charge experiment that caused stalling of the hydrogenation reaction steps and accumulation of hydroxylamine intermediate. It would however have been better assessed by systematic evaluation of reactions run with planned and controlled hydrogen deficits to potentially curtail hydrogenations at each intermediate step of the hydrogenation reactions for rigorous safety evaluation of each of the reaction intermediates that could be generated with deteriorating hydrogen mass transfer efficiency on scale up.

It is also important with scale up of hydrogenations to ensure that hydrogenator reactor design is optimized for efficient hydrogen gas mass transfer from headspace to liquid and then to the catalyst (for example using a gas re-entraining agitator) so as to achieve efficient onward conversion of nitro to hydroxylamine to amine whilst ensuring conditions are chosen to ensure a sufficient safety margin between operating conditions and thermal runaway conditions both for the starting material and for the hydroxylamine intermediate.

Consultation of Bretherick's (*12*) is, as ever, also a good source which also highlights the risks of increased instability from incomplete nitro reduction (*cf.* Volume 2, Catalytic Nitro Reduction Processes section).

The Isochem example emphasizes the general point that DSC or ARSST testing of reaction mixture stability should ideally be done at the start, at the end and at points in between, through the course of reaction to ensure that the stability of all reaction mixture compositions, comprising starting materials, products and potential build up of intermediates, are all checked for stability before concluding that the safety margin between planned reaction conditions and onset-temperature for thermal runaway is sufficient, especially if energetic materials are suspected for starting materials, intermediates or products.

The Stoessel Failure-Scenario Criticality Tool for Ranking of Reaction Hazard Risks

The relative safety of the preceding Isochem chloronitroaromatic hydrogenation reaction scenarios can be considered with the help of the Failure-Scenario Criticality ranking tool developed by Francis Stoessel for chemical reaction hazards risk evaluation (*20*, *31*, *32*).

The Stoessel Failure-Scenario Criticality ranking tool (also commonly referred to as the Stoessel Diagram, *cf.* Figure 25) helps the assessment of reaction hazard risks based on the relative placement of four critical reaction criteria:

(i) The planned operating temperature - referred to by Stoessel as $\mathbf{T_{process}}$ or $\mathbf{T_p}$

(ii) The maximum adiabatic reaction temperature attainable for the planned reaction (aside from unwanted secondary reaction decomposition exotherms) – referred to by Stoessel as **MTSR**, the Maximum Temperature of the Synthesis Reaction.

(iii) The solvent boiling temperature for a system open to atmosphere or, for closed systems, the boiling temperature corresponding to the maximum operating pressure before opening of a pressure relief valve, or rupture of a bursting disk, or any other practical temperature limit for the reactor system in question – referred to by Stoessel as **MTT**, the Maximum Temperature for Technical reasons.

(iv) The onset-temperature for thermal runaway. This is depicted by Stoessel with an ill-defined lower boundary since initiation of thermal runaway can vary according to methodology and circumstances, as explained below. All temperatures above the thermal runaway onset-temperature are increasingly dangerous so that thermal runaway onset is depicted in the Stoessel Diagram as a continuous bar extending upwards from the runaway onset boundary.

Stoessel depicts the thermal runaway onset range with an ill-defined lower boundary for a number of reasons: First of all, because measurement of thermal runaway onset-temperature can give variable results, depending on the equipment and conditions used, influenced by equipment sensitivity and speed of temperature ramp during runaway-onset measurement. Also, because a reaction mixture held under adiabatic conditions may continue to self-heat in the event of reactor cooling failure, e.g. if unreacted, but still reactive, reagents accumulate and continue to react in the mixture, or if other exothermic reaction steps continue to occur. Hence reaction mass temperature can continue to increase after a cooling system failure, even if no further reagents are added. Stoessel accordingly defines the maximum safe temperature limit (depicted as the lower boundary of the thermal runaway onset bar in Figure 25) more cautiously than the thermal runaway onset-temperature measured by DSC or ARSST. He defines this reaction temperature safety limit (denoting the maximum safe temperature without risk of thermal runaway, even with cooling failure) as the maximum temperature up to which the $\mathbf{TMR_{ad}}$ (the Time to Maximum Rate of the thermal runaway/decomposition under adiabatic conditions) is greater than 24 hours. Stoessel denotes this temperature $\mathbf{T_{D24}}$. In other words, if temperature is maintained below $\mathbf{T_{D24}}$ then even if cooling fails at large scale (such that essentially adiabatic conditions prevail) and even if accumulated reagents are still present in the reaction mixture that continue to react and liberate heat, the reaction mixture will only continue to heat so slowly that thermal runaway won't be accessed within the time period of 24 hours from the moment of cooling failure. This 24 hour period then allows ample time for cooling failure (or other plant malfunction compromising heat removal) to be noticed and for corrective actions to be taken to terminate self-heating (such as implementation of backup power, alternative cooling, reaction quench or other measures to compensate for, or to terminate, the reaction exotherm), as depicted in Figure 24.

Of course there is no special significance behind the choice of 24 hours as the time limit dictating the maximum safe temperature below which a reaction mixture won't continue to exotherm to thermal runaway within the 24 hour period. It is simply that 24 hours is a sensible time period for recognizing and responding to potentially unsafe modes of failure. This response time period should be tailored to reflect circumstances in terms of the particular reaction system in question and the realistic ability to detect and to respond to control failures. Defining a shorter time period than 24 hours within which a reaction won't access thermal runaway (*i.e.* time to maximum rate under adiabatic conditions of < 24 h) allows for a higher maximum safe operating temperature but dictates the need for greater responsiveness for detection and remediation of reaction control or cooling failures. Conversely a lower maximum safe operating temperature threshold is necessary if a longer time period than 24 hours is required to detect and respond to reaction control failures. Determination of reaction mixture stability and $\mathbf{T_{D24}}$ requires that worst case reaction mixture stability must be tested. Hence samples should ideally be taken and tested for stability (by DSC and/or ARSST) at various times during the course of potentially exothermic reactions, or (for reactions having unstable starting materials, intermediates or products) with potentially exothermic decomposition pathways, to ensure that the worst case reaction mixture is identified.

The truly safest maximum reaction temperature then is the temperature at which a reaction mixture will not continue to self-heat to reach thermal runaway conditions, even in the absence of cooling and even over an extended period of time such as 24 h. This criterion (**T_{D24}**) of the maximum temperature for time to maximum rate under adiabatic conditions (**TMR_{ad}**) of > 24 h is a far more stringent test than a thermal runaway onset-temperature typically measured by DSC or ARSST with a fast temperature ramp rate (of > 1 °C / min). This is because a fast temperature ramp rate determines the point at which temperature and rate of temperature rise reach their maximum values over a period of minutes rather than within 24 h, further undermined by limited sensitivity of calorimetry equipment. This all serves to emphasize the importance of repeating DSC and ARSST measurements at slower temperature ramp rates of around 0.5 °C /min to determine a more accurate onset-temperature once an initial onset-temperature is identified by a faster temperature ramp rate of say 2 to 4 °C /min, since a fast ramp rate can otherwise overshoot the true thermal runaway onset-temperature giving rise to a false degree of confidence. Thermal runaway onset-temperature measurement by DSC or ARSST further underestimate thermal runaway risk because such instruments exhibit a minimum threshold detection sensitivity below which an exotherm is not registered. This means that thermal runaway onset is not detected until a higher temperature is reached than the true onset-temperature. A thorough evaluation of maximum safe temperature without thermal runaway could be achieved by holding reaction mixture samples under adiabatic conditions at different temperatures for each sample over 24 h to determine the true onset-temperature for accessing thermal runaway within a 24h period. The same conclusion can however be extrapolated from simple DSC or ARSST data and by using computed isoconversional methodologies to model heat release rate as a function of temperature and conversion; refer to chapter 11 of Professor Stoessel's Thermal Safety of Chemical Processes book for further details (*20*).

The Stoessel Diagram (Figure 25) uses the relative positions of the key temperature characteristics referred to above to classify reactions from Class 1 to Class 5 where Class 1 is the least dangerous and Classes 3 to 5 are all potentially very dangerous. Class 1 reactions are of least concern because the worst case adiabatic temperature rise does not reach the thermal runaway onset-temperature and the heat of vaporization of the reaction mixture solvent then serves as an additional energy barrier between the maximum adiabatic temperature and the thermal runaway onset-temperature.

The Class 2 scenario is only slightly more risky as it still has maximum adiabatic temperature rise below thermal runaway onset-temperature but without the additional buffer of the solvent vaporization energy sink between the two.

The Class 3 scenario is substantially more hazardous, however, as the solvent boiling temperature is below the maximum adiabatic temperature rise so that loss of cooling would result in some or all of the solvent boiling out of the reaction mixture. In such cases it is imperative that:

(i) any adiabatic temperature rise calculation includes estimation of how much reaction solvent would be lost by evaporation

(ii) testing be done on reaction mixture stability with thermal runaway onset-temperature after loss of the estimated amount of solvent, since bimolecular (and higher order) reactions will accelerate with increasing concentration. This, in turn, is likely to cause increasing rate of heat output and lowering of the thermal runaway onset-temperature.

A further potential concern is to determine the maximum rate of solvent evaporation to ensure that this can be accommodated without reactor pressurization during full scale plant engineering design.

The Class 4 scenario is very dangerous since the adiabatic temperature rise can access the thermal runaway temperature, albeit moderated to some degree by solvent vaporization absorbing heat. In this case multiple measures and controls are necessary to ensure appropriately sized and engineered cooling and backup cooling systems are present, ideally with low process inventory, if this scenario cannot be avoided.

The Class 5 scenario is potentially the worst of all where the adiabatic temperature rise, *e.g.* with loss of cooling, can access thermal runaway conditions without even solvent heat of evaporation to absorb energy and help prevent a catastrophe!

The order of safety between Class 3 and Class 5 is not definitive since highly energetic reactions or decomposition pathways can exacerbate the dangers of the lower classified systems.

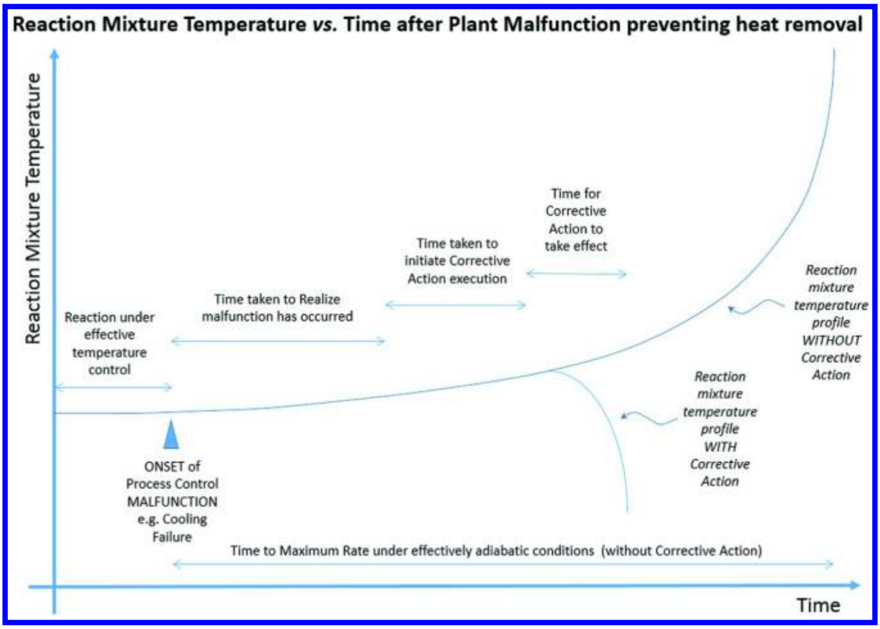


Figure 24. Illustration of reaction temperature vs. time with, and without, corrective action, after plant malfunction preventing heat removal

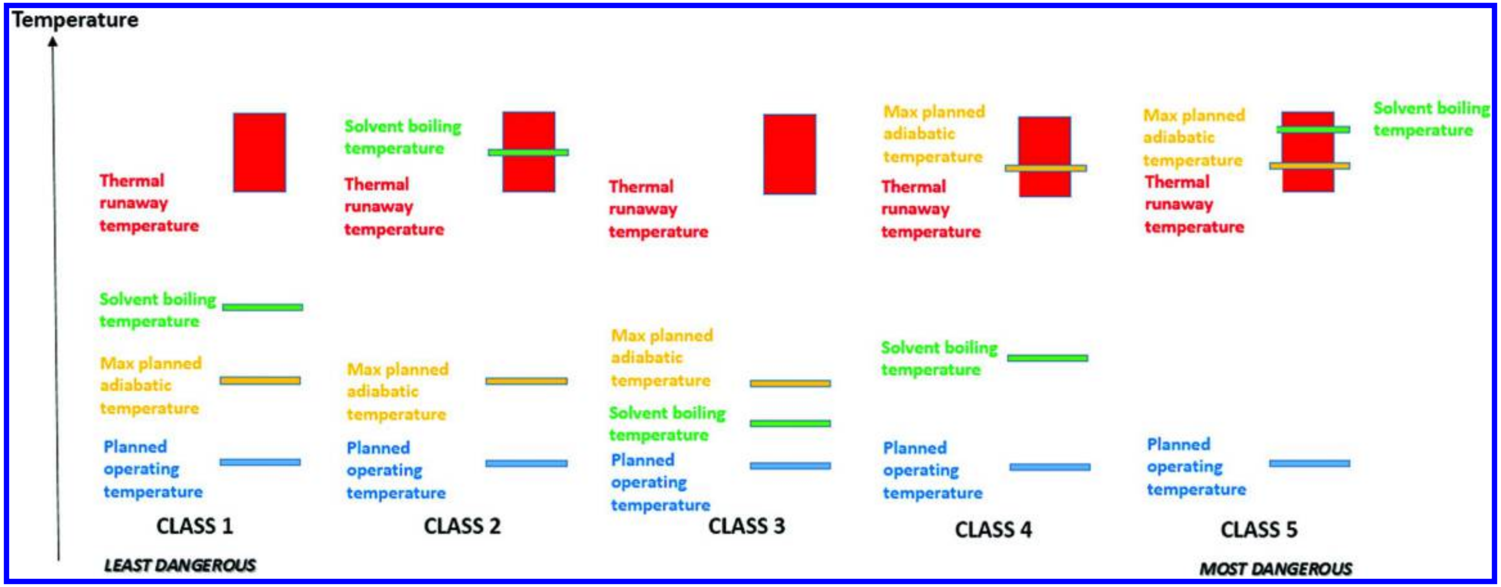


Figure 25. Adapted from Stoessel Diagram (20, 31). Note that the Thermal runaway temperature is denoted as a shaded block indicating that thermal runaway can initiate over a range of temperatures, with the lower limit of this block depicted by Stoessel as an indistinct line due to variability in determining this boundary; Solvent boiling temperature equates to Stoessel MTT; Max planned adiabatic temperature equates to Stoessel MTSR (see color insert)

In cases where reaction classification by the Stoessel Diagram relies on heat dissipation through solvent vaporization, one must keep in mind that the solvent boiling point temperature assumes atmospheric pressure. If, however, operating pressure is raised above atmospheric pressure (as was the case with the T2 Laboratories explosion, described earlier, where a pressure relief valve was set too high), then solvent boiling temperature is also raised above its atmospheric boiling temperature which may remove an important safety factor. Hence the T2 explosion incident falls into Class 5 since the elevated boiling temperature of the solvent under the autogenic (self-generated) pressure arising after cooling failure allowed the resulting adiabatic temperature rise to access the thermal runaway onset-temperature without the intervening tempering influence from solvent heat of vaporization to help prevent the thermal runaway.

The Stoessel Diagram is helpful in prompting analysis of intrinsic safety and in encouraging process and reaction system design to avoid Class 3, 4 and 5 conditions and to try to achieve Class 1 conditions wherever possible. For instance, by increasing reaction mixture dilution so that heat capacity of solvent serves to mitigate adiabatic temperature rise or by exploring lower boiling solvent and/or higher solvent heat capacity options to help prevent access to higher temperatures where thermal runaway risks exist.

Caution is however still necessary even with the least risky scenario classes. For example, in cases where solvent heat of vaporization is insufficient to fully absorb adiabatic temperature rise or when the runaway decomposition energy release could be so fast as to rapidly vaporize solvent leading to reactor pressurization and elevation of solvent boiling temperature before pressure relief, giving rise to risk of explosion at worst and loss of containment with release of solvent to the environment at best. The deteriorating efficiency of mixing on scale up also needs to be taken into account with fast exothermic reactions. Localized high concentration of reagents can give rise to localized accelerated reaction rate and localized heating beyond the safe limits determined by macroscopic calorimetry measurement of reaction mixtures as a whole. Hence a significant safety margin of 100 °C or more (*33*) is appropriate between the planned operating temperature and thermal runaway onset-temperature. Alternatively, extensive additional measures should be taken to mitigate the risk and/or the consequences of thermal runaway (such as rapid reaction quench availability or adoption of continuous reaction technologies with low inventory and high heat transfer cooling efficiency). For highly exothermic reactions and/or those with significant thermal runaway risks, additional measures are needed to anticipate and mitigate risk for which professional safety assessment is necessary.

Applying the Stoessel Diagram tool to the Isochem reduction scenarios in the previous section above shows that the original Isochem safety data (generated for the end of hydrogenation reaction mixture with a full catalyst charge, even though this did not represent worst case conditions) is apparently consistent with the least risky Stoessel Diagram “Class 1” category. This is because their measured worst case (adiabatic) temperature rise (*i.e.* in the absence of any reactor cooling) equated to a maximum temperate of 80 °C planned operating temperature plus 41 °C adiabatic temperature rise = 121 °C maximum temperature for their desired synthesis reaction which is below the solvent boiling temperature of around 150

°C under the planned reaction conditions and is even further below their measured onset-temperature for thermal runaway of 280 °C.

The more relevant Isochem data that they measured for their incomplete hydrogenation reaction (obtained with a stalled reaction from half catalyst charge) however gave an increased adiabatic reaction temperature and an onset-temperature for thermal runaway below the solvent boiling temperature, increasing their reaction risk classification, according to the Stoessel Diagram, from Class 1 to Class 2 or even higher!

Hence the Stoessel Diagram is a useful tool for prioritizing attention to reaction safety risks, ranked according to the Diagram's classifications, with a view to changing reaction conditions to mitigate Stoessel Diagram reaction classification ratings or, where that is not possible, then ensuring adequate engineering controls to mitigate the risks associated with the higher classifications.

Control of Heat Evolution Rate on Scale Up

Reaction calorimetry (measured for example using Mettler Toledo RC1 or HEL Inc Simular calorimeters) is helpful and can be essential in confirming and quantifying heat of reaction. Use of RC1 or Simular calorimeters, with around 500 mL or greater scale glass reactors, are appropriate once extremely energetic thermal runaway reactions have been ruled out (through knowledge of stability and/or DSC or ARSST testing of reaction mixtures).

Although the magnitude of the heat released is very important, further risk can also be associated with the *rate* at which heat is released. Calorimetry and thermal runaway onset measurement (by ARSST or DSC) can give some understanding of magnitude and the rate of heat evolution. Once a thermal runaway initiates then control is generally no longer an option because reaction rate and heat evolution rate accelerate with increasing temperature (see Arrhenius equation above). This gives rise to an exponentially increasing reaction rate, heat generation, solvent vaporization, pressurization and explosion risk. Hence intrinsic reaction control by control of reagent addition (and with confirmation of no substantial reagent accumulation) is essential with energetic systems that are highly exothermic and/or have highly exothermic unwanted decomposition pathways. This is necessary to prevent encroaching near to thermal runaway conditions.

Even if a good safety margin between operating temperature and thermal runaway onset-temperature is apparent through labwork and small scale calorimetry, there is always also the risk that poor mixing or poor heat transfer on scale up can give rise to increased localized concentration or increased localized heat generation, respectively. To address these concerns, stress testing of reaction mixtures is appropriate (when an excess of one reagent over another is present). Whilst these steps are necessary for safety considerations they are also sensible for product quality, considering the potential impact on quality that could arise from localized higher concentrations of one reagent over another or localized higher temperatures through poor heat transfer on scale up.

The impact of localized increased concentrations of reaction by-products on reaction outcome, as well as process safety and control, should also be considered. Many examples exist of deteriorating reaction selectivity on scale up. For example, addition of a solution of sodium hydroxide to neutralize an acid salt of an amino lactone may work fine at small lab scale (with efficient mixing, mass transfer and heat transfer) but may result in lactone hydrolysis on scale up due to localized elevated hydroxide concentration and localized heating at the point where the reagent makes contact with the bulk reaction mixture. Similarly, during ester formation by addition of an acid chloride to an alcohol for ester formation, complications and adverse consequences can result from localized HCl generation on scale up. Even oven drying needs to be considered and evaluated carefully with scale up since heat transfer and mass transfer from the middle of a thick cake of material is less efficient than that from a thin layer of material in a lab drying oven. Hence the exposure of product to residual solvent at elevated temperature can be protracted on scale up compared with lab operation giving rise to potential concerns if the extended time/temperature exposure with residual solvent on large scale drying gives rise to unwanted chemical reactions. This should be checked by stress testing product with residual solvent present in sealed pressure-compatible vials (rated for safe containment of autogenic solvent pressure *vs.* temperature) using a lab oven.

In fulfilling the requirement for intrinsic reaction control, as discussed previously it is a dangerous misconception to assume that an exothermic reaction can be best controlled by maintaining a colder reaction temperature. In practice this can have the opposite effect on scale up when colder reaction temperature allows for accumulation of reactive reagent(s) which can then give rise to an uncontrolled exotherm on scale up once the reaction initiates. It is always best with exothermic reactions to ensure full exotherm control by controlled addition of preferably the most reactive reagent at such a rate and temperature at which the reagent is substantially consumed within the time needed for efficient mixing of the added reagent, typically a minute or more at larger scale. This can be confirmed by evaluating the reaction kinetics as a function of temperature at lab scale using calorimetry or by ReactIR reaction monitoring, or sampling and HPLC analysis of reaction kinetics. With the reaction kinetic data in hand, if the large scale reaction mixture temperature rises because the heat of reaction exceeds the heat transfer capabilities for heat removal, the situation can be easily and quickly remedied by throttling back or suspending addition of the controlling reactive reagent. The reaction selectivity also needs to be checked if the reaction temperature is increased from that adopted for prior lab work to ensure that a higher reaction temperature does not introduce unwanted reaction pathways through overcoming energy barriers for those unwanted pathways.

If an adequate safety margin between desired operating temperature and thermal runaway onset-temperature of 100 °C or greater cannot be achieved, then more stringent multiple precautions are needed to ensure that the reaction mixture temperature cannot under any circumstances approach thermal runaway conditions even at the localized point of reagent addition. Multiple fail-safe means for reaction cooling may be appropriate under such circumstances with the possible need for rapid reaction mixture dilution or release to a quench tank in the event safe operating conditions are exceeded. All possible scenarios during risk assessment should be considered, including power, cooling and/or agitation failure consequences, as well as redundancy in temperature measurement. Prompt definitions of appropriate mitigating actions for each scenario should be put in place in line with the probabilities and impacts.

In situations where the reaction exotherm is significant and thermal runaway consequences are severe, continuous process technology is sometimes the only safe solution. In this case a continuously fed and continuously discharged small reactor can achieve large scale throughput. This also provides the safety advantages of very efficient heat transfer (through small scale continuous reaction processing, with close proximity of reaction mixture to relatively large surface area reactor walls, compared with the low surface area : volume ratio with batch reactor design) so that tight temperature margins can be maintained. Continuous processing can also be beneficial in limiting the active inventory of unstable chemicals within the reaction zone to as small a quantity as possible. Hence, in the unlikely event a thermal event were to occur, the energy that would be released from the reactor would be relatively small and the consequences would be manageable. Such continuous technology approach has been used successfully in continuous preparation and use of diazomethane without accumulation of any appreciable inventory between generation and consumption of this extremely toxic, volatile and unstable reagent (*34*).

Operational Hazards

In addition to intrinsic chemical reaction hazard anticipation, it is imperative to give attention to potential operational hazards that could be introduced as a result of process accommodation and execution within manufacturing equipment. An obvious requirement is to endeavor to avoid flammable or explosive atmospheres within chemical manufacturing equipment. If this is not possible, then efforts should be made to avoid any possible source of ignition by excluding at least one vertex of the fire and explosion triangle. Combustion and/or explosion risks are introduced if all three components are present (Figure 26). Dispersion and confinement further contribute to the risks of an explosion with handling of flammable dusts so that these two additional parameters are then referred to, in combination with the aforementioned three parameters, as the dust explosion pentagon.

If flammable solvents are used then it is important to ensure that oxygen ingress is precluded and air is displaced by an inert gas, such as nitrogen, so that oxygen content is maintained outside of the explosive range for the solvent vapor that is present. Beware of the risks of atmospheric oxygen ingress whenever chemical reaction vessel integrity is compromised. Even taking a sample of a reaction mixture under nitrogen blanketing introduces a very real risk of oxygen ingress and flammable atmosphere generation within the headspace of a reactor. Introduction of a sampling cup into a reactor through an open reactor port pulls with it a pocket of air in its wake, giving rise to the risk of localized flammable or explosive atmosphere generation in the vicinity of the sampling location. It might appear as if this would be of no concern in the absence of an obvious source of ignition but with non-electrical-conducting non-polar solvents in particular there is always a risk of static electricity generation whenever solvent movement takes place (*e.g.* with solvent pumping, transfer or mixing). Fast moving non-electrically-conducting solvent in an electrically non-conducting or ungrounded tube can readily give rise to a substantial electrical field and a literally shocking electrical discharge through visible and audible sparking to the nearest electrically grounded point. Similar static generation can occur when solvent is stirred within an electrically-non-conducting (e.g. glass) vessel. In the words of Trevor Kletz, a pioneer of chemical process risk assessment (*35*): "ignition sources are the only thing we get for free in the chemical industry"!

Sampling during product crystallization in toluene (a non-electrically-conducting solvent) within a glass reactor can give rise to a sudden small exotherm and generation of potentially carcinogenic benzopyrans resulting from a small amount of air ingress and ignition of the resulting air and solvent vapor by static electricity generated by stirring of the crystallization mixture. In addition to the safety hazard, this can cause unacceptable contamination and the need for batch disposal or rework, despite continuous blanketing nitrogen gas flow into the reactor throughout the reaction mixture sampling operation. As well as static electricity, heat from friction within the reactor agitator seals or inadequately lubricated bearings can also serve as a source of ignition so that the safest process design is to ensure that flammable gas or vapor and/or oxygen concentration (dictated by measured or reported lower explosive limit, LEL) is always outside of the lower and upper explosive limits for the flammable solvent being used by means of nitrogen blanketing and exclusion of opportunities for air ingress. Monitoring the percentage of oxygen in the reactor atmosphere may be required to ensure that explosive limits are avoided.

All metal equipment and transfer pipes must be electrically connected and grounded to prevent buildup of static electricity, especially when pouring or transferring a non-electrically conducting solvent from a metal container to a reactor or other vessel. It is important not to overlook the possibility of static charge generation with portable equipment such as metal barrels during charging or material transfers so these should be electrically grounded with a clamp and heavy gauge wire connection. Non-conducting equipment cannot be grounded effectively but use of a surrounding electrically grounded wire mesh can at least mitigate buildup of electrical charges on the outside of the equipment. Flammable solvents should be handled either in a flameproof area (where electrical equipment is housed in purged enclosures to prevent exposure of flammable vapors to electrical sparks) or within a fumehood where adequate airflow is maintained to keep solvent vapor concentrations below lower flammable limits.

Addition of solids to a reactor containing flammable gas or vapor is another operation requiring rigorous atmospheric oxygen exclusion. For example addition of reactive metals (such as magnesium or sodium) or reactive metal hydrides (such as sodium hydride or lithium aluminium hydride) to reaction mixtures that generate hydrogen gas during reaction or decomposition should only be carried out with rigorous air exclusion. This can be achieved by deploying a double butterfly-valved charge chute whereby the top valve can be opened for solids introduction followed by top valve closing, tube purging with nitrogen and only then bottom valve opening to allow solids to be charged into the reactor without risk of oxygen ingress to the headspace containing solvent vapors and hydrogen gas. Slurry charging from a nitrogen purged agitated feed vessel is another option.

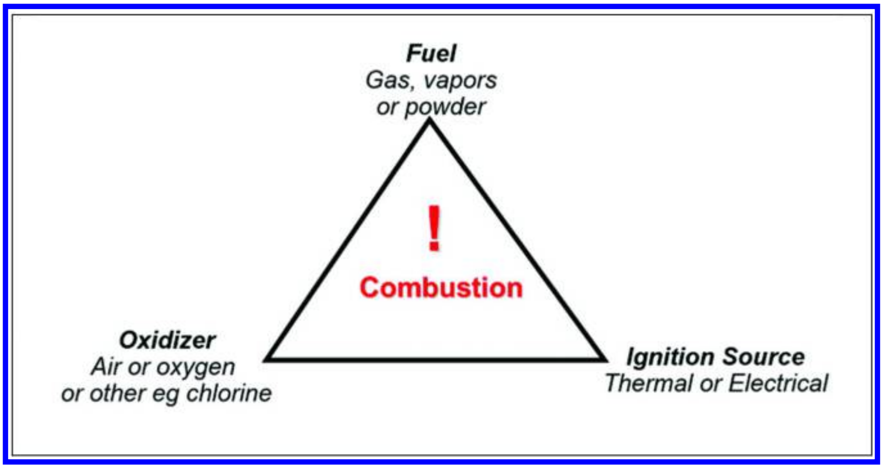


Figure 26. Explosion Triangle (see color insert)

Where non-condensing flammable gases are generated (such as hydrogen from use of sodium hydride as a base or butane from quench of DIBAL, for example) it is important to dilute the flammable gas below its lower flammable concentration limit before release to atmosphere or else to purposefully burn it (after a flame trap) at the point of discharge to avoid the risk of accumulation and ignition of a flammable gas cloud. Hydrogen gas leakage is a particular danger wherever it is used, since it can collect in roof voids in a manufacturing facility due to its buoyancy in air and can give rise to a flammable or explosive pocket of gas that could be ignited by static electricity, heat or even sunlight (*36*).

Consider the hazards of all materials that are being used and are produced in reactions, such as the fate of the *iso*-butane generated on workup of the DIBAL reduction example described above. Various examples of catalytic hydrogenation have also been discussed above in the context of their chemical reaction hazards. In addition to these chemical reaction hazards, catalytic hydrogenations can also introduce operational hazards. This is due to the pyrophoricity of the dry palladium on carbon or platinum on carbon or Raney Nickel catalysts so that such catalysts are typically supplied wetted with water to suppress pyrophoricity. Problems with catalyst handling can nevertheless occur when hydrogenations are carried out with water miscible non aqueous solvents such as methanol or ethanol since non-pyrophoric water wet catalysts are stripped of their water in such reaction systems. Hence when reaction mixtures are sampled for in process control testing, with removal of catalyst by filtration, or when catalyst is removed from product by filtration prior to workup and product isolation, the catalyst that is filtered off is then devoid of water and is instead wetted with volatile flammable solvent. As the residual solvent evaporates on the filter, the drying platinum or palladium on carbon is then prone to spontaneous combustion in air which can represent a significant fire hazard in proximity with flammable reaction solvents. Smaller scale laboratory fires have also occurred when such catalysts are disposed of inappropriately in trash cans or other receptacles open to the air!

It is appropriate to recognize the pyrophoricity of isolated platinum on carbon or palladium on carbon catalysts and to ensure that such materials are immediately wetted with water on isolation before exposure to air.

Oxidation reactions with oxygen gas releasing reagents such as hydrogen peroxide or indeed with air itself are also clearly a source of hazard if undertaken with use of flammable solvents. Diligent oxygen monitoring is necessary during lab work and scale up of such reactions to ensure that oxygen concentration is maintained below the lower explosive limit for the solvent system being used. Methylene chloride is typically assumed to be non-flammable but even this solvent exhibits flammable limits and is flammable above 100 °C when present at concentrations between 12% and 19% in air.

Bretherick's Handbook (*12*) highlights potential safety concerns in handling peroxides and other chemicals such as hydroxylamine, particularly if destabilized by transition metals. It is important to ensure that absolutely no contact with ferrous and other transition metals is possible when peroxides and other such materials are handled, stored or transferred within manufacturing facilities to prevent catalysis of dangerous reactions. This requires rigorous review of all plant materials of construction covering not only the obvious materials such as transfer lines and vessel walls but also less obvious materials such as thermometer pockets, connector pieces, brackets and seals. This evaluation should also include "what if" consideration of whether *e.g.* proscribed materials could become exposed if other materials fail (such as sealing gaskets in lines). Peroxide monitoring, and reductive quench if necessary, should be adopted when handling peroxides or peroxidisable materials, especially on distillative removal of peroxidisable solvents such as ethers. This is because peroxidised solvents are less volatile than the parent solvent itself so that the derived unstable peroxides can end up being concentrated and energetically decomposed in still residues during distillative removal of the parent solvent.

Operational hazard risks also exists with oven drying if flammable solvent and air are present and vapor is not reduced to below the solvent lower explosive limit before heat is applied. Hence it is best to displace air with inert nitrogen gas and to evacuate before applying heat during oven drying.

Even something as seemingly innocuous as a lab scale cryogenic vapor trap in-line to protect a vacuum pump can give rise to a serious explosion hazard if liquid nitrogen is used and the vacuum manifold system is left open to atmosphere after use. A liquid nitrogen bath will cause condensation of liquid oxygen from air within the condenser tube and the combination of liquid oxygen with previously condensed organic materials can give rise to an explosive mixture as it warms up after use!

Highly energetic materials (for example those flagged as energetic by DSC, oxygen balance or other tools) should also be evaluated by testing for shock sensitivity. Appropriate precautions should then be adopted for safe handling to avoid imparting sufficient energy for decomposition through physical shocks during material transfer. Serious accidents can otherwise occur, even at relatively small laboratory scale, as with the January 7th 2010 explosion at Texas Tech University Chemistry and Biochemistry Department when a graduate student was seriously hurt with loss of three fingers, eye perforation and burns from detonation of just a few grams of an energetic nickel hydrazine perchlorate derivative he was stirring in hexane on an open bench without a blast shield, eye goggles or other appropriate safety gear (*37*). A photograph taken after the explosion shows the fractured bench and the extent of damage (Figure 27).

Figure 27. Aftermath of Texas Tech lab explosion. Photograph courtesy of U.S. CHEMICAL SAFETY AND HAZARD INVESTIGATION BOARD, taken from CSB Case Study NO. 2010-05-I-TX (38)

Diazonium salts as non-isolated intermediates can be sufficiently stable for chemical processing if kept in solution (for example in the Sandmeyer conversion of aromatic amines to haloaromatics) but industrial explosions have occurred when diazonium salts come out of solution, for example when splashes of reaction mixture on reactor walls dry out and then decompose energetically initiating bulk reaction mixture decomposition.

Deteriorating mixing efficiency on scale up can give rise to process hazards and explosion risk. For example, when nitration reaction mixtures stratify due to density differences and poor agitation in large scale reactors. This can result in unintended extreme concentration in the lower phase and poor heat transfer of the viscous medium which can represent a serious process hazard that can also result in an explosion.

Combustible solid materials can also give rise to dust explosion risk if such dusts are allowed to accumulate on surfaces exposed to air. Any vibration, gust or movement can subsequently result in a flammable dust cloud which, once ignited, then causes flame propagation as the initial gas expansion causes more and more dust to become airborne and ignite. This occurred with devastating consequences in the 2008 Port Wentworth Georgia sugar refinery explosion (Figure 28) which left 14 dead and 42 injured (*39*).

Figure 28. Aftermath of Port Wentworth Georgia sugar refinery explosion

A more recent dust explosion incident occurred on 2nd August 2014 at a car parts factory in Kunshan, Jiangsu Province in Eastern China where 75 people were killed and 180 were injured by a metal dust explosion at a car parts factory (*40*). This was caused by ignition of accumulated dust from milling and polishing alloy car wheels which generated a fireball of burning metal dust. Even otherwise unreactive metals can demonstrate spontaneous ignition and flammability if present in very fine particles surrounded by air as the author recalls from a childhood school chemistry lab experiment demonstrating the auto-ignition of nano-sized particles of colloidal "pyrophoric lead (*41*)" when sprinkled in air (where high surface area, reactive surface and air friction resulted in lowering of ignition activation energy with relatively spectacular, albeit toxic, results)!

Even chemical identity can be a safety-critical aspect of a process. An example of this is provided by an explosion that occurred on 3rd October, 1996 at the Avonmouth Works of Albright & Wilson when a chemical delivery tanker containing sodium chlorite was wrongly documented as containing epichlorohydrin due to a labeling mix up by the delivery contractor. The tanker was accordingly directed to discharge its sodium chlorite contents into the epichlorohydrin bulk chemical storage tank causing a highly exothermic reaction within the storage tank, pressurization due to boiling of the epichlorhydrin (b.pt. 118 °C) and explosion (*42*).

An explosion in 2003, killing 8 people, similarly occurred due to mixing of incompatible materials at an Indian chemicals facility when acetic acid was added to a road tanker containing a residue of concentrated nitric acid from a prior load that had not been cleaned out effectively before loading the acetic acid. This incident was no doubt caused by exothermic generation and energetic decomposition of acetyl nitrate, followed by ejection and combustion of the acetic acid (flashpoint 40 °C) (*43*).

Other Safety Considerations

Assessment of process risks should also consider any and all other potential adverse implications arising from process operation, including operator safety and impact on the environment. Measured toxicity data should be taken into account to ensure that containment measures are adequate to avoid exposure of process operators or others in or around a manufacturing facility to unsafe levels of toxic materials. This should ideally be achieved by engineering controls through design of manufacturing facilities to achieve containment. Engineered containment is augmented by the implementation of backup measures comprising personal protective equipment such as protective clothing, gloves, boots, dust masks, safety glasses, safety shields, helmets or even supplied air breathing equipment where necessary.

Toxicology and physical forms of toxic materials should be considered (for example whether in vapor form, dusty solids, or liquids) as well potential routes of exposure (through inhalation, skin contact, eye contact or ingestion) to guide design of appropriate equipment and procedures to ensure containment and operator protection. Inorganic cyanide for example exerts little vapor pressure when dry but it exists in equilibrium with toxic gaseous hydrogen cyanide vapor when wet and when exposed to non-basic conditions (near or below hydrogen cyanide pKa of 9.2).

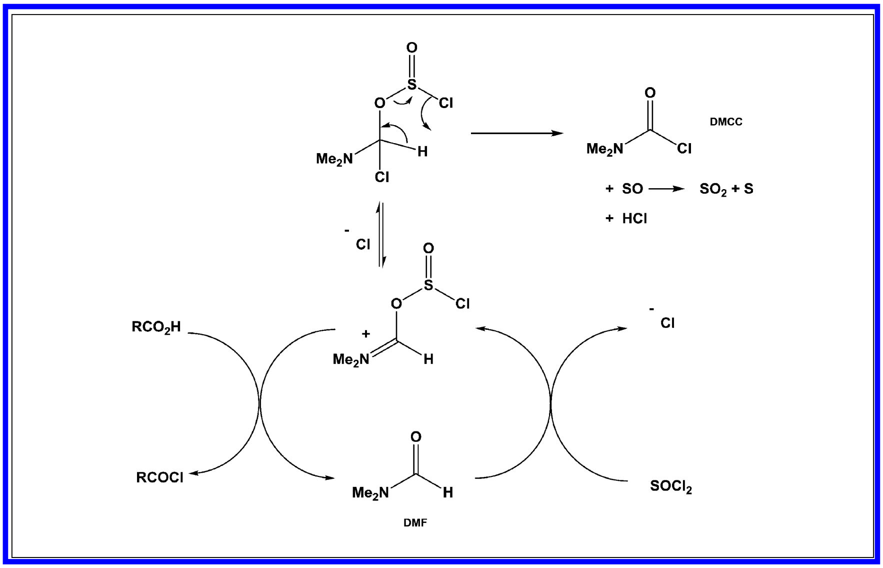
Work to quantify the mass balance for formation and reaction of an acid chloride to try to improve on yield losses encountered during scale up led to identification of dimethylcarbamoyl chloride (DMCC) as a minor reaction by-product (*45*). This by-product was attributed to reaction of the DMF reaction catalyst with the thionyl chloride reagent for acid chloride generation, followed by redox decomposition. This becomes a significant reaction pathway especially towards the end of reaction where the carboxylic acid substrate is largely depleted allowing redox chemistry generating DMCC to compete with acid chloride formation (Scheme 17). The carcinogenic nature of DMCC was recognized, which initiated the development of sensitive analytical methods capable of monitoring DMCC presence down to its threshold limit value (*44*). DMCC downstream fate was tracked and it was destroyed in process waste streams. Taking these measures protected the process operators from exposure to DMCC, and a warning was published regarding the risks of DMCC in all reactions using DMF as a catalyst for acid chloride formation as well as in Vilsmeier formylation chemistry (*45*, *46*).

Impact of processes on the environment must also be considered to ensure safe disposal of all process waste streams whether gaseous, aqueous, solid, or incinerated liquid waste. Appropriate testing of disposal protocols are required to confirm safety of all discharges to the environment. The environmental effects may be direct *e.g.* fish toxicity of aqueous waste after treatment or indirect *e.g.* toxicity of exhaust gases from a waste incineration facility. A complete mass balance is necessary to determine all reaction by-products with adoption of scrubbing and/or detoxification as well as environmental monitoring wherever appropriate. Typical examples include employing an alkaline bleach scrubber to contain and destroy acidic vapors, cyanide monitoring where cyanide might be generated, the use of a refrigerated condenser and caustic scrubber as well as environmental monitoring into and out of the scrubber where methyl or other volatile alkyl halides are generated. Volatile organic vapors should be contained for incineration, recycled by cryogenic condensers or destroyed by use of thermal oxidation at the point of vapor release.

Different waste streams should be confirmed to be safely compatible before they are combined. Typical requirements include the segregation of strong acids from bases, reducing agents from oxidisers, cyanide salts from acid, acetone containing solvent waste from chlorinated solvents especially if pH is basic (*47*), as well as methanol containing aqueous waste from bleach (see the discussion of oxygen balance and Equation 4 above) (*48*). It is good practice to inspect any packaged waste streams to ensure that they are not generating heat or gas pressure over several days before sealing for dispatch to ethical disposal facilities.

Aqueous effluent discharged to the environment must be treated to remove toxicity and to neutralize oxygen demand with testing before discharge to confirm compatibility with aquatic species.

Toxicity and environmental impact abatement are beyond the scope of this chapter so that further research of these topics should be undertaken concerning the specific toxic components involved with the particular reaction systems under investigation.



Scheme 17. Generation of dimethylcarbamoyl chloride from synthesis of acid chloride with $SOCl_2$ and DMF

Hazard and Operability (HAZOP) Studies

The hazard and operability study (HAZOP) methodology was developed within Imperial Chemical Industries (ICI) in the UK in the 1970's to provide a framework to guide evaluation of "what if" scenarios by considering all possible variations for all aspects of a chemical process and hence necessary mitigation of any with dangerous consequences. Descriptions of the methodology can be found online (*49*). HAZOP is also encouraged for pharmaceutical quality risk management by Good Manufacturing Practices guideline ICH Q9 (*50*). HAZOP is a useful discipline for exhaustive consideration of likely safety concerns, especially for plant design to accommodate potentially dangerous processes. It does rely on the thorough knowledge and understanding of all safety related aspects of process and plant by participants. There are times though when the very systematic (and potentially somewhat tedious) rigorous HAZOP approach to consideration of all possible circumstances and their permutations can serve to discourage the more creative thought processes that are *also* necessary for identification of less obvious but potentially equally critical hazards and risks so that creative-thinking-oriented brainstorming of potential risks is also recommended in addition to HAZOP studies.

Another useful expedient in preparing for scale up of manufacture is to establish a safety, quality and general planning checklist of all necessary requirements for manufacture. This should include confirmation that the process has been defined giving acceptable product quality, that sufficient raw materials of requisite quality have been obtained and confirmed acceptable, that specifications are in place, that hazards have been determined, that a basis of safety has been defined, etc. This can then be reviewed at a multidisciplinary pre-manufacturing discussion along with stepwise consideration of written batch instruction sheets to prompt "what if" brainstorm-style questioning of any and every situation that could adversely affect process safety and product quality (as a less comprehensive but nevertheless effective HAZOP analysis).

Whatever tools and methodologies are used, there is a need for a thorough review, by one means or another, to establish the basis of safety for large scale manufacture including all necessary supporting data. Procedural controls also need to be in place to ensure safety, with a formal sign off of a documented safety summary by those involved with and responsible for, process design, plant design, quality confirmation and manufacturing execution, along with sign off by safety management and senior management bearing overall responsibility for safe operations. This confirms that necessary process safety assessment steps have been taken to demonstrate diligence in formal ownership of safety responsibility.

Summary and Recommendations

The job of a process chemistry organization is not only to achieve efficient conversion and selectivity to give desired products in high yields and high purities, with robustly-scaleable chemistry generating minimal waste, at lowest possible cost and without intellectual property impediments, *but* it is *also* to effectively anticipate *everything and anything* that could possibly go wrong with a proposed manufacturing process so as to allow definition of appropriate measures to safely mitigate all such eventualities!

Recognizing that heat is much harder to remove on scale up of even mildly exothermic reactions is an important first step. Hence significantly exothermic reactions should, wherever possible, be safely controlled by regulated addition of one or more reactive reagent(s) so that the heat of reaction can at any time be curtailed by suspending reagent addition. Analytical procedures should be developed and used to prove that suspension of addition does indeed curtail heat of reaction without preceding reactive reagent accumulation. Addition of reagents faster than they can react is only appropriate where it can be proven that the worst case adiabatic temperature rise is benign because either:

- the heat of reaction is insufficient to boil off reaction solvent and cannot remotely approach thermal runaway onset-temperature, or
- the reaction rate is so slow that heat removal can easily be achieved, notwithstanding poor heat transfer characteristics of larger scale reactors (and again with no accelerating exotherms accessible under adiabatic conditions).

It is appropriate for process chemists and manufacturing colleagues to consider all possible eventualities and failures that could potentially give rise to hazardous situations and to then implement appropriate measures to prevent such eventualities taking place.

Bond energies give an indication of heats of reaction but can overlook effects of solvation or phase changes. Any chemical transformation that is assessed by structural analogy, oxygen balance, Bretherick's Handbook (*12*), ARSST and/or DSC as significantly exothermic or resulting from using reactive or unstable materials or combination of materials should also be assessed by calorimetry. This will determine the actual heat of reaction and potential adiabatic temperature rise to model the worst case of heat transfer inefficiency on scale up. Reaction calorimetry should be measured in addition to determining thermal runaway onset-temperature in the case of reactive or potentially unstable systems (e.g. using DSC and/or ARSST) to ensure a well-controlled safety margin between proposed operating conditions and unsafe conditions. It is also necessary to recognize that localized concentrations and temperatures (with deteriorating mass transfer/mixing and heat transfer on scale up) may exceed planned parameters for the bulk mixture as a whole.

Risk analysis should be used to rank potential risks according to likelihood of occurrence and consequences of occurrence with mitigating measures designed and deployed to prevent all but the least significant risks.

Controlled slow addition does not necessarily equate to effective reaction control without reaction mixture analytical data (using ReactIR or sampling and HPLC or better still reaction calorimetry) to confirm (with exothermic reactions) that slow addition is indeed preventing accumulation of energetic reagents as well as any reactive intermediates. Actual lots intended for large scale manufacturing operation should ideally be verified in the laboratory for both safety and derived product quality before use in manufacture, especially where raw material quality variation could affect safety or quality (*e.g.* with magnesium where particle size distribution and extent of oxide coating has a significant bearing on reactivity and induction period before onset of reaction).

Potential hazards linked to operational design and use of manufacturing equipment should also be considered in addition to potential chemical reaction hazards covering planned as well as possible unintended eventualities.

A useful discipline is to define the "basis of safety" for process scale up. A checklist of necessary provisions for safe manufacture can also be helpful, as is a detailed hazards and operability analysis, carried out with multidisciplinary representation by all those contributing significantly to process design and manufacturing implementation. A formal procedure for sign off of all processes before scale up is necessary to demonstrate diligent corporate ownership and execution of process safety responsibility.

Many resources are available to help safe process design including:

- process safety publications (notably Bretherick's Handbook of Reactive Chemical Hazards (*12*)
- Stoessel's Thermal Safety of Chemical Processes (*20*)
- *Organic Process R&D* journal safety issues as well as this book
- process safety consultants (including Dekra Chilworth Technology https://www.chilworth.com/contact-us/ , HEL Inc http://www.helgroup.com/contact/ , Swissi Process Safety GmbH http://www.swissips.com, and Fauske & Associates http://www.fauske.com/contact-us, as well as safety consultant individuals that can be found by internet search or by general consultation with organizations such as Scientific Update https://scientificupdate.co.uk/).

These resources can all assist with process safety data generation and interpretation, as well as review of manufacturing intentions for any and all potentially hazardous operations.

Above all, remember: *"safety doesn't happen by accident"!*

Disclaimer

Check with professional safety advisors to obtain formal hazards assessment and risk analysis before scale up of any (and especially any potentially energetic or dangerous) chemical reactions since guidance offered within this chapter cannot be generalized to cover unanticipated situations or needs.

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Dr D Levin, Norac Pharma, Azusa, CA, USA; 25th September 2014

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Chapter 2

Safety by Design, The Bedrock for Managing Process Hazards

Tony Y. Zhang* and Sean P. Lapekas

Small Molecule Design and Development, Eli Lilly and Company,
Lilly Corporate Center, Indianapolis, Indiana 46285
***E-mail: zhang@lilly.com**

This article aims to emphasize the importance of incorporating safety as a basic element in the design stage of chemical processes, as safety designed-in is inherently superior to safety realized by processing parameter control. The practice of safety by design is an organic aggregate of creativity in route design, thoroughness in risk identification, and fundamental understanding in reaction mechanisms. Examples are given to illustrate that process safety does not have to come at the expense of process efficiency and product quality. The Safety by Design thinking is summarized as twelve principles for managing process hazards.

A well-designed chemical process shall enable the manufacturing of the desired compound with high quality in an efficient, consistent, and sustainable manner. Process safety is the very foundation for achieving this goal. Because of the flammability of most organic compounds, even simple organic processing has inherent risks. Additional risks are introduced as transformation from one substance to another inevitably involves exchanges in energies among the molecules involved and their environment, with potential not only for side reactions, but also intended reactions with unintended kinetics and unpredicted thermal output. While significant progress has been made at minimizing work-related injuries and fatalities, largely due to the established and continually refined systems at identification and management of risks, and implementation of preventive measures, there are still too many accidents involving the use of organic chemicals.

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A long history of fine chemical processing has helped to shape both the regulatory systems by various government entities and common practices by the industry communities (*1*, *2*), interludes of unfortunate incidents notwithstanding. Innovations in material science, sensor and control technologies have contributed to improved design and construction of equipment and plant sites. Advancement in fundamental organic chemistry and popularization of reaction calorimetry have led to better understanding of reaction thermodynamics and more thorough assessment of critical processing parameters. Modern analytical techniques such as on-line mass spectrometry, in-situ IR and in-situ NMR have greatly facilitated the interrogation of reaction mechanism and transient intermediates. Application of process analytic technologies (PAT) has enhanced the level of monitoring and control of large scale chemical processing. Despite this progress, chemical accidents still occur (*3*). While a majority of accidents involved human errors or mechanical failures that could have been prevented, design oversight also contributed to a significant number of them (*4*).

The purpose of chemical processing is the selective transformation of one compound into another in an efficient manner. Selectivity and reaction efficiency are achieved with favorable thermodynamics which is provided either by changes in the physical (e.g. temperature) environment or chemical (e.g. reagent, catalyst) inputs. To deliver commercially acceptable efficiency and selectivity, excess in energy or reagents are often applied. A good process designer seeks to strike the right balance between the quest for selectivity, efficiency and the fundamental need for reliability and safety. This challenge is not unique to the chemical industry. In fact, many other professions have developed time-tested practices to manage safety which could be very beneficial for chemists and engineers to adopt and extrapolate for chemical processing. Commercial aviation, for example, is another heavily regulated industry with high inherent risks, when one considers the challenges associated with lifting an object made with millions of parts, weighing more than 200 metric tons (half of that being highly flammable hydrocarbons upon take-off) up to an altitude of a few kilometers for hours. However, the fact that modern aviation has a safety record better than automobiles if measured by per passenger- mile traveled speaks for the triumph of integrating science, engineering, training and business systems. First, an average driver's education is no comparison to the rigor of training programs for commercial pilots. More important is the extra level of robustness designed into the aircraft. Just like designing requirements for an aircraft requires a trust to the constancy of certain principles such as atmospheric composition, gravity and fluid dynamics, a well-designed chemical process rests on the fundamental understanding of thermodynamic principles of all ingredients involved. The aviation industry has done exceedingly well in developing a systematic approach toward passenger safety which includes the quality system of aircraft maintenance, pilot training, and standard operating procedures specific to aircraft types.

In several industries, the "Swiss Cheese Model" has been widely used to illustrate the risk management principle and human error analysis, with the momentary alignment of holes representing the confluence of factors culminating to the eventual accidents (*5*). Adaptation of key elements of the same metaphor to chemical processing might lead us to an illustration shown as Figure 1. There could be layers of barriers between a root cause (e.g. the flame) and the eventual accident. By interactive gaps we mean peculiar combinations of two or more parameters which may lead to an edge of failure nonobvious and non-intuitive by single parameter trend analysis. Reducing the size of each individual hole (deviation/defect) and increasing the layers (redundancies) of preventive measures, or changing location of the holes (isolation) are reasonable risk management strategies. Execution of such strategies should begin with the inherent hazard assessment of the synthetic route followed by definition of the operating boundaries of the associated unit operations).

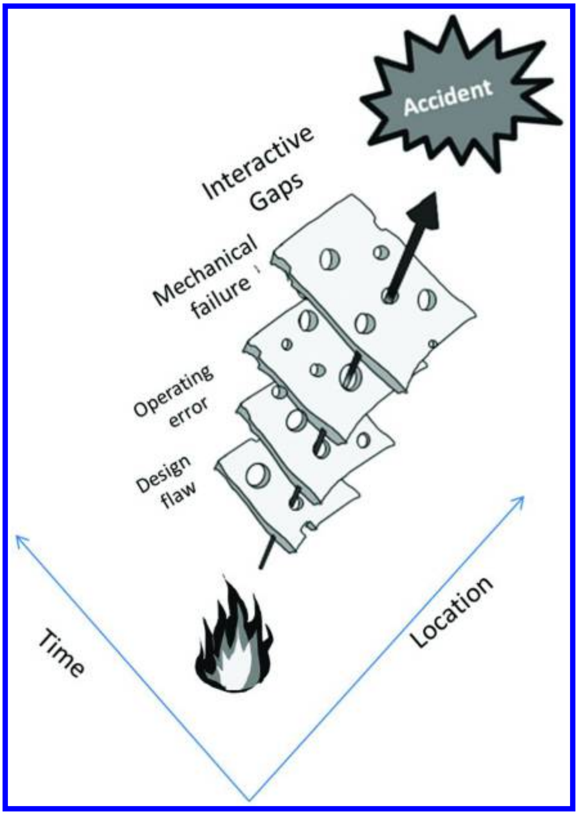


Figure 1. The Swiss Cheese Model of Process Accident

Because of the diversity of chemical processes, especially those involving pilot plant development, where the scale is large enough for the consequence to be grave, but processing parameter variability remains high, ***safety by design***, rather than safety by learning from failures, becomes imperative in modern chemical process development.

Readers in the pharmaceutical industry may find the term “Safety by Design” a vernacular strikingly similar to the Quality by Design (QbD) (*6–8*) framework for managing qualities of pharmaceutical products. As a pillar of US FDA’s 21st Century Pharmaceutical Quality Initiative, QbD is a systematic approach to product and process development that begins with predefined objectives and emphasizes product, process understanding and process control based on sound science and quality risk management. This is opposed to the traditional Quality by Testing paradigm, where product quality is mainly ensured by a series of testing on raw material, intermediates and the final product. Under QbD, development of a pharmaceutical manufacturing process begins with Process Design, followed by Process Qualification, and continuous refinement by Process Validation before being installed for commercial manufacturing. The criticality of the process parameters and quality attributes thus are usually established at the Process Design stage based on sound understanding of the process and risk assessment to product quality.

Process safety is unquestionably a critical part of any manufacturing process, and is the prerequisite for any quality control mechanism. While Quality by Testing of the final products had been the pharma industry norm for many years, safety by testing the final outcome of the process has never been an affordable approach. Understanding the process mechanistically and specifying the safe operating parameter boundaries has been an approach that has withstood the test of time for managing risks in chemical process development. In this sense, practice of Safety by Design might have preceded QbD due to necessity for many years.

There are many excellent articles and regulatory guidance on the subject of QbD (*9*, *10*). The key philosophy can be delineated briefly as follows: (a) Definition of desired product quality outcomes; (b) Design and development the manufacturing processes to achieve these outcomes; (c) Identification of critical quality attributes (CQA); (d) Identification and controlling sources of variability with critical processing parameters (CPP) and proven acceptable ranges (PAR), and (e) Monitoring and modifying the process to ensure consistency. The emphasis on design and validation serves the ultimate goal that if it the process is designed well and operated within the boundaries defined by the CPPs, product quality is a natural outcome. While deviation in manufacturing process may not necessarily lead to failure of the final product meeting specifications, deviation in process execution may well disqualify or put the product batch on hold under the GMP quality system. Like QbD, Safety by Design is not only about the establishment and definition of the operating platform with enough buffering capacity to deliver safety as the definitive outcome, but more importantly it has to do with designing an inherently safer process that relies less on control and testing for the desired outcome (Figure 2).

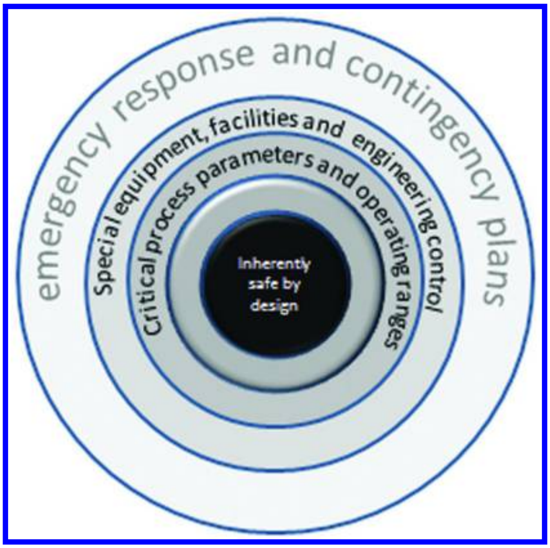


Figure 2. Approaches to Process Safety

The QbD mantra "quality cannot be tested into products, i.e., quality should be built in by design" remains accurate if one replaces the word "quality" with "safety." The best way for achieving product quality is having the manufacturing process designed so that high quality product is the most natural outcome across wide operating ranges. If quality can't be designed in, then it can be achieved with controlling the operating parameters to narrower ranges. The last resort for ensuring quality is by testing of the final product. For process safety, the best approach is also inherent safety by design, with added layers of protection by operating parameter control, SOPs, and other engineering controls as needed.

Safety by Design begins early in the development phase with assessing the hazards of the raw materials to be used for each synthetic route option (*11*). In general, the more benign the chemicals are, the lower the risks there will be for processing those chemicals. However, the need for the necessary reactivity of the chemicals to effect the desired transformations has to be considered. The next step is to qualitatively compare the conditions required to execute the desired chemistry, and balance the reactions. The more extreme the conditions (high or cryogenic temperatures, high pressures, large excesses of reagents, long reaction time), the higher the risks will be upon scale-up.

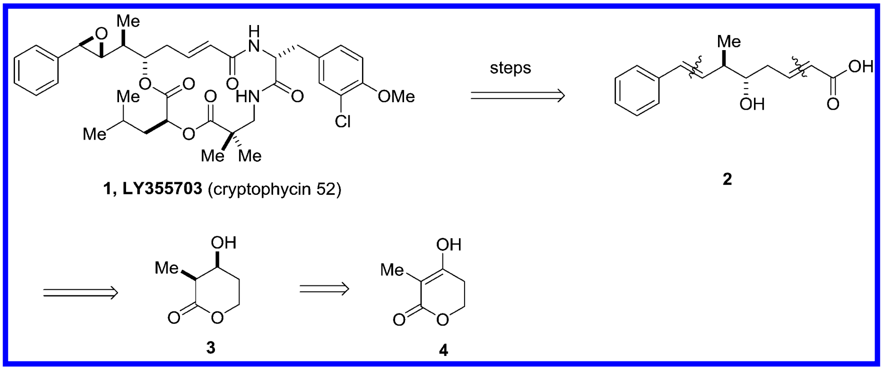
When balancing reactions, special attention should be paid to potential generation of gaseous by-products for both the desired reactions and unintended decompositions. Lastly, the reactivity of the reagents towards anything they come into contact with should be considered. If a reagent has the potential to react violently with a large number of other materials used elsewhere in the process, or in the manufacturing facility (*12*), additional controls will be required upon scale-up to prevent inadvertent mixing with incompatibles. At Lilly, our Chemical Hazards Lab has developed an Inherent Safety Index (ISI) Tool to assist process chemists in performing this assessment during synthetic route design and selection activities. Using data often available from a safety data sheet (SDS)

(*13*, *14*), and a chemist's general knowledge, the ISI Tool compares the inherent safety characteristics of competing route options in six hazard classifications:

- Flammability
- Vapor-Air Explosiveness
- Toxic Release
- High Energy Groups
- Reaction Hazards
- Chemical Hazards and Incompatible Reactivity.

In addition to comparing overall scores, the route options are overlaid on a Radar plot for quick visual analysis of each category (*15*).

We'd like to use the following example to illustrate the principle of Safety by Design and utilities of Inherent Safety Index (ISI). Compound **1** (LY355703) (*16*) has been a clinical candidate as a microtublin inhibitor for anticancer indications. It is an analog of a natural product cryptophycin originally isolated from blue green algae. As part of a program at developing a scalable process, it was discovered that that **1** could be most efficiently prepared from enollactone **4** (Figure 3).



1, LY355703 (cryptophycin 52)

2

3

4

Figure 3. Process for LY355703

While structurally being extremely simple and possible to synthesize in a one-pot manner, preparation of **4** involved demanding reaction conditions using commercially available 2-methylacetoacetate (**5**, Figure 4). Because a hydromethylation is required at the distal methyl carbon of the substrate, it entailed a dianion formation using hygroscopic and pyrophoric agents NaH and *n*-BuLi. The reaction had to be carried out under very dilute conditions as the sodium salt of the first enolate (**6**) tends to become a gel in THF. The process also gave off flammable gases (hydrogen and butane), was sensitive to oxygen and moisture, and required cryogenic conditions. The reaction was not only low yielding but also inherently difficult to operate. An ISI analysis of this process was conducted and an overall score of 59.25 was obtained, largely contributed by the reaction hazards and flammability of THF (solvent), butane and hydrogen (byproducts).

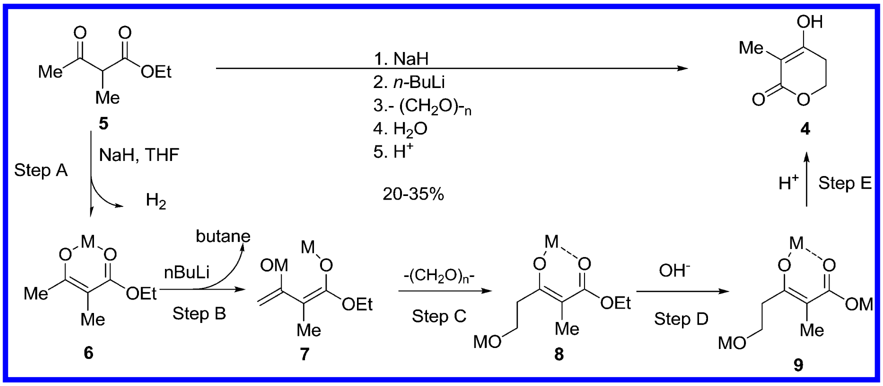


Figure 4. Original Enollactone Process

Mechanistic studies revealed that the key reason for the low yield of the reaction stemmed from the low effective concentration of the electrophile formaldehyde, as trapping of dianion **7** (M = Na or Li) by other electrophiles (e.g. ArCHO) did afford the intended addition product in high yield. While there have been multiple reports on the generation of monomeric formaldehyde at the condensed state for improved activity, these were impracticable due to either the requirement for high dilution or instability for large scale processing. Rapid repolymerization into paraformaldehyde ensued upon holding the monomeric form. Elevated temperature or protic solvents would favor the formation of the monomeric form. However these conditions were not compatible with the dianion **7**. Additionally, dianion **8** also proved unstable, and due to the locked geometry of the chelated cation, it would not cyclize into the product unless the ester underwent sequential saponification and neutralization with an acid (Step D and E). By this mechanism, process safety could only be achieved through vigorous control of reaction parameter such as temperature, oxygen, moisture, addition rate and sequence, and venting of flammable gases. A safety by design effort was thus initiated and resulted in an improved process (Figure 5) (*17*).

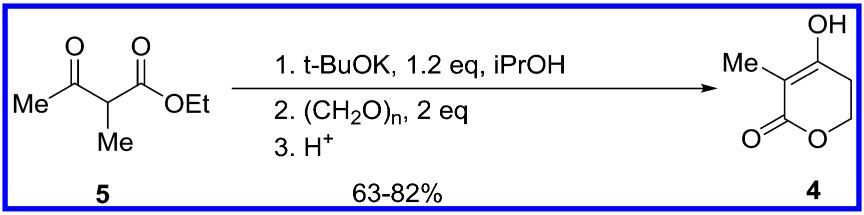


Figure 5. Improved Enollactone Process

While both processes are very similar in starting material and product, the mechanisms are totally different. The new process is much simpler to operate, utilizes the same starting material, but goes through a totally different set of intermediates. It never needs to go through the unstable dianions, and does not give off flammable gases. It actually goes through two more steps but most of them are taking place near equilibrium conditions, with the reaction outcome entirely driven by thermodynamic and in a one-pot fashion, without the need for overtly reactive species (Figure 6).

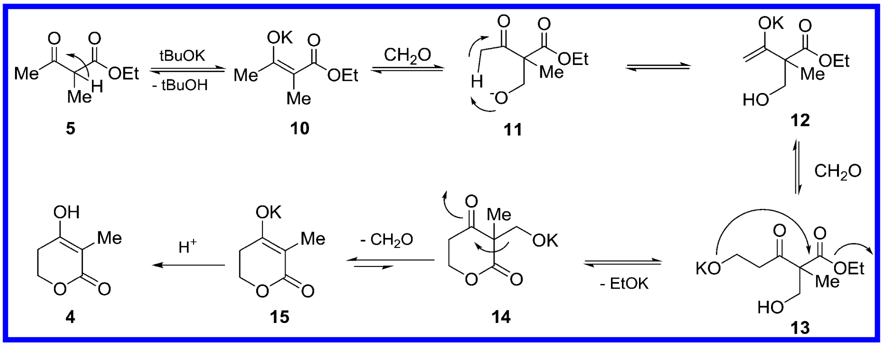


Figure 6. Improved Process with Safety Designed-in

An analysis by the ISI Tool provides a graphical illustration of the improvement in inherent process hazards, shown in the following radar plot (Figure 7). Significant reduction was achieved in the high energy groups and reaction hazards category and incompatible reactivity category, and the overall score was reduced by over half.

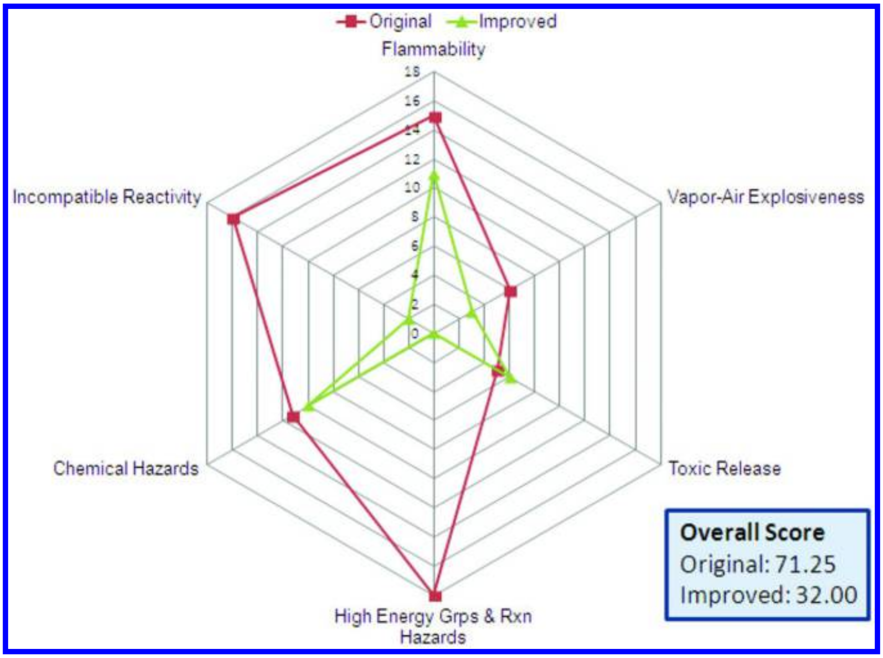


Figure 7. Before and after, Inherent Safety Index for the Enollactone Process

To summarize, we have compiled the following key elements for designers of chemical processes to consider when designing for safety. While some of these were derived from our own experience and internal learnings, many are generally recognized principles and widely adopted practices by industrial colleagues:

1. **Design "genes of inherent safety" into the synthetic route.** If operating errors (stemming from gaps in organizational culture, poor training or lack of adherence to SOPs etc.) and equipment failures are the external factors leading to accidents, flaws in process design can be considered as inherent defects, like genetic aberrations waiting for the right conditions to express and manifest. There may not be a simple answer as to what are the "genes" for a safe process, but synthetic routes that are simple and aesthetically pleasing to the architects of process chemistry usually have them. Seamless integration of transformations with just the necessary amount of external energy usually affords the simple elegance of a well-designed and safe process. The simpler the process, the safer it usually is.
   Ideally a safe and simple process should consist of few reaction steps driven by thermodynamic equilibria without using brute force. It can tolerate wide operating ranges and remains robust and durable enough to withstand the test of time, manufacturing scale and locales, fluctuations in raw material supply and advancement of science and technology. This is also the common criteria for judging the durability of a synthetic route (*18*). It tends to be devoid of repetitive reductions/oxidations (*19*) and protection/deprotection cycles. With respect to available reaction types, a skilled process designer usually favors those with common safety features such mild and forgiving reaction conditions. The Dieckmann condensation (*20*), for example, remains one of the tried and true methods for making cyclic compounds in the industry. Besides affording product ketoesters as versatile intermediates for further functionalization into heterocycles, it has the following desirable features: (a) it is driven by a thermodynamic equilibrium, forming the more stable β-ketoester; (b) it only requires moderate external heating and relatively mild bases; (c) it is easy to commence and stop the reaction; (d) it tolerates a wide range of substrates; (e) the byproduct is benign; and (f) it is not prone to adverse thermal events.
2. Develop **mechanistic understanding** for every reaction step in the process early during investigation, explore all possible side reactions/side products, and evaluate their impact to process safety. This includes material compatibility of storage containers and process equipment. A systematic checklist is very useful at identifying latent risk, e.g. an autocatalytic side reaction or participation of solvents. With the increasing availability of modern instrumentation such as in-situ IR, reaction kinetics can be interrogated not only by monitoring the starting material and product concentration, but also by the relative rate of the formation and disappearance of reactive intermediates. These insights will greatly aid the reaction system design so that the side reactions

can be managed to an acceptable extent with appropriate intervention measures such as addition rate and sequence, stoichiometry, temperature and efficient removal of side products, especially gaseous ones.

3. Thoroughly assess the **thermal stability** of the materials used in the process. This is particularly important for compounds that contain known high energy functional groups. Look for compounds that may be susceptible to catalytic decomposition by other reagents/impurities or construction materials of the equipment, and test as necessary.
4. Establish a **material balance** for all transformations, identify any gas generation potential and explore behaviors of reagents and solvents under stressed storage and reaction conditions. It is especially important to determine the fate of any excess reagents used in the process that are of high energy or high reactivity in nature, or possessing gas generating potentials. There have been multiple accidents due to insufficient accounting of the fate of all chemicals. Examples include mixing of incompatible chemicals in the waste collection systems, generation and accumulation of heavy metal azides in metal pipes, or allowing cyanide salts to mix into acidic solutions. It may be necessary to develop additional processing steps (including assays to verify the destruction) for neutralizing excess reagents prior to disposal, if avoiding excess is not feasible.
5. Establish an **energy balance** for all reactions in the processing equipment. This includes obtaining heats of reaction and adiabatic temperature rise through either calorimetry (preferred), or theoretical modeling (depending on resource availability and complexity of the reaction), knowing the heat transfer characteristics of the processing equipment, and establishing a robust **control of the reaction rates**. Numerous accidents were caused by failure to recognize that changes in processing conditions could result in the heat generation rate exceeding the heat removal capacity of the equipment. This problem also occurs when scaling up as the reactor's surface will not increase as fast as the volume, reducing the ability for heat removal. Achieving an addition rate-controlled exotherm to manage the heat generation is a common approach, which is predicated on acceptable reaction kinetics. A control mechanism that can be easily turned off (*e.g.* pump, heat, light) to stop the reaction is an ideal way to manage reaction rate.

   A number of past incidents involving the formation of Grignard reagents are mostly due to poor initiation kinetics and the accumulation of halides in contact with large amount of magnesium metal. Application of proper activators, catalysts, reaction temperature, and concentration are common solutions to avoid the accumulation of reactive species. Reaction suppression (e.g. free radical scavengers, extinguishing fires using halon) is possible but acceleration of reactions by catalysts to an appropriate rate so that heat transfer can be managed safely is generally preferred (catalyst should never be added to mixtures of reactants).
6. **Avoid the accumulation of high energy species** among starting material, isolated intermediates and products. The synthetic route

should be evaluated holistically to include unstable, highly energetic (e.g. NaN_3) and polymerizable starting materials or intermediates, and this has to be examined across the whole projected production life cycle. Safer alternative and surrogates should be diligently sought. In addition to safer alternatives, on site production/usage, and **continuous processing** (*21*) of reaction and hazardous and reactive species have also been widely adopted in the industry.

7. **Minimize excess** in reagent or energy input. In a typical batch process, as the reaction approaches completion, concentration of reactants drops, so does the rate for higher order reactions. Excess reagents or elevated temperature are often applied to drive the last few percentage of remaining starting material into product. This need has to be balanced with the risks associated with the use of excess reagent, energy and substrates, as all excessive forces and reactive chemicals have to be neutralized/dissipated safely one way or another. In addition, excess reagents may also lead to side reactions with the product whose concentration is increasing as reaction progresses.
8. **Avoid or reduce the use/isolation of highly active or potent compounds** of carcinogenic, mutagenic or reproductive hazards. Considerations should be focused on the ultimate functions by these reagents or how they contributed toward the synthesis, so as to explore safer alternatives in the holistic design. For example, phosgene, while being extremely toxic, used to be the essential and low cost reagent for making polycarbonates from diols and/or bisphenols as an active and anhydrous carbonic acid equivalent. The polycarbonate industry, for example, has gone through the transformation of making, storing, transporting and using phosgene to less hazardous alternatives such as on-site generation and immediate use of phosgene from chlorine gas and carbon monoxide. Ultimately we believe the industry will move toward the much safer and greener process of directly using carbon dioxide to supply the carbonyl and using ethylene oxide as dehydrating agent or other means of activation.
9. Develop a good understanding of the **capabilities and limitation of manufacturing equipment**, communicate design philosophy with engineers early to integrate appropriate and orthogonal **safety redundancies** (process analytics, sensors, monitors, vent sizing etc.) into new designs of processing equipment.
10. Perform rigorous **process hazard reviews**. Critical reviews of the chemical process must be carried out to identify and evaluate potential hazards and their impact to process safety and product quality. Iterations of the design shall be followed to reduce the risks to an acceptable level against all possible scenarios under a production setting, which can be very different from the more controlled developmental pilot plant (*22*, *23*). Review panel members shall be experienced, from varied backgrounds (scientists, engineers, safety officers, operators), objective, inquisitive and independent from undue business pressure. Hazard identification involves the thorough understanding of the following:

a) Nature of the process, especially material and energy balance, and possible side reactions, b) Capabilities and limitation of all the equipment involved, including sensing and control instrumentation, and c) Appropriate level of redundancies and emergency response system and business contingency plans.

11. Build a **culture of safety** (*24*) with training and retraining (after a certain period of time) of scientists, engineers, and operators with case studies and involve them in investigations of incidents and near-misses. The Heinreich Principles of Accident Prevention (*25*) states that for every major injury-causing accident, there are approximately 30 or so accidents that cause minor injuries and 300 that cause no injuries. Since many of the accidents share common root causes, minor accidents and even near misses provide much bigger datasets for analysis of the common root causes and design flaws in equipment, process flow, training programs and operating procedures. For the lack of a better indicator, the number of near misses may serve as a surrogate for measuring whether a workplace has established a culture of safety and the robustness of its safety systems.
12. **Learn from mistakes and other professions** (e.g. aviation) on risk management and refine best practices to continuously improve process hazard manage systems. Learning by one's own mistakes is an expensive proposition, however learning from accidents happened elsewhere is an efficient way to broaden one's knowledge base (*26*, *27*). The National Chemical Safety Board maintains an excellent archive of completed reports on accident investigations (*4*), which are highly recommended reading for chemists and engineers engaged in chemical processing.

Among these principles, it is worth to emphasize the importance of establishing **dose-controlled exotherms** for managing reaction heat (No. 5 and 6). Many hazardous unit operations were managed with acceptable safety record by applying this principle. A classic example is the complete oxidation of gasoline within internal combustion engines. An aerobic oxidation process is happening thousands of cycles per minute at high temperature with huge pressure swings, and yet these events are managed safely because the amount of fuel and initiation for each explosion can be controlled precisely, and the reaction heat can be removed accordingly with equipment designed with high safety coefficients.

In summary, we recognize the synergy between the Quality by Design principles and process hazard management and feel that design for safety needs to be emphasized at the outset and as the foundation for quality and productivity. Processes with safety designed into them will tend to have the level of consistency required for product quality. There is much to learn from other industries on creating a culture of safety by design. The chemistry community can also contribute to the societal need for balancing productivity with safety with examples from our industry on designing safety into the manufacturing processes.

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Chapter 3

Strategies for Safely Handling Industrial Azide Reactions: The Three Traps

Thomas Archibald[*]

Technology Consultants, 1909 Beach Drive SE, St. Petersburg, Florida 33705
[*]E-mail: Archibaldmail@gmail.com

Industrial use of azides requires special care to avoid explosions or poisonings. Life-cycle management of azide is discussed from the time azide-containing material is received at the front gate, sampled and stored, moved to the plant, placed in reactors, and finally until all wastes are abated and all equipment decontaminated. Key failure modes resulting from inadvertent isolation of extremely dangerous hydrazoic acid or other azides are described. Recommendations are made for control and containment of azides in a multi-purpose plant. Operational discipline, which includes operator training, plant maintenance and change control, is highlighted as a critical safety element.

Introduction

This review offers guidelines for operating industrial azide reactions after the safety of the reaction chemistry is understood (*1–3*). Reactions containing azides need increased attention and skills, particularly on commercial scale. But azide chemistry is not capricious, and its dangers can be readily understood and handled. Azide's notoriety comes from small-scale laboratory experiments whose safety is often poorly understood. As a result, accidents occur and scientists hear only about the deleterious results of using azide. Scientific safety studies have usually been focused on reaction chemistry and product stability, issues that are rarely troublesome in a manufacturing setting. Less attention has been paid to dangers which arise from control and containment of azide. Clearly for industrial use, a holistic approach to the procurement, use and disposal of azides is best. The focus here will be on a life-cycle approach for large-scale operations.

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What follows is a compilation of the author's personal experiences and general knowledge, and is designed to illuminate the areas where workers have traditionally run into difficulties. Unlike laboratory incidents which are often published, manufacturing incidents are generally not reported outside of legally mandated channels. Companies will investigate and remedy problems but will rarely publish either the incident or its cause because its process may involve trade secrets or confidentiality. Companies using azide chemistry will also not discuss their practices because of liability concerns. As a result, information that could prevent recurrences of hazardous operations and events is not disseminated. This chapter has as a goal to cover as many of these potential problems as possible.

Sodium azide has a rich chemistry for introducing functionality into molecules. With the advent of "Click" chemistry (*4*), the number of publications using azide reactions has grown rapidly, and consequently so has the number of laboratories. Annual scientific citations to azide has increased by 300% from 2000 to 2013 to over 4000 per year. Azide chemistry has also become an integral part of pharmaceutical manufacture as shown by increased numbers of target compounds potentially requiring its use, for instance zidovudine (AZT) for HIV/AIDS or tetrazole-containing sartins such as Irbesartan (Figure 1).

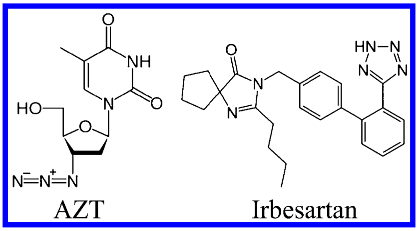

Figure 1. Structures of zidovudine (AZT) and Irbesartan

The usefulness of azide reactions is limited by the threat of hazardous events, as intermediates and reagents can be both explosive and toxic. Therefore, safety considerations for such reactions require high priority. Once operational parameters and appropriate equipment have been designed, then operational discipline (training and change control) becomes the key to safe operations.

To understand the safety requirements and procedures for handling, reacting and abating materials containing inorganic and organic azides, this review should be seen only as a starting point. It does not substitute for a detailed safety review for each process. Even for chemistry that has been run before, there will be something different in the next permutation to be run and as will be shown, insignificant changes can lead to disaster. Information should be continuously updated to incorporate lessons learned, new technologies, and suggestions for improvements as they are discovered. Since these reactions are often done in a multi-purpose facility, particular care must be paid to changes in the facilities, procedures, or quantities. A good place to start will be to discuss three situations that this author has found to be common problems when working with azides.

Three Traps

Most incidents result from one of three "traps" inherent in the nature of azide chemistry. These traps are well known to "specialist" companies working with azides, but are often inadequately understood by scientists without extensive experience with azides. Understanding the nature of each trap can help workers understand and avoid them.

The three traps are:

(1) The ease of formation and accidental isolation of concentrated solutions of hydrazoic acid.
(2) The uncontrolled handling of azides permitting formation of solid metal azides.
(3) The unintended formation or isolation of low molecular weight organic azides.

Each trap will be discussed in detail to show how sometimes traps can work in combination.

Trap 1: Hydrazoic Acid

Hydrazoic acid is an extremely dangerous material both as a liquid and in vapor phase; it is both highly toxic and explosive (*5*). Few compounds possess such a combination of acute dangers as hydrazoic acid. Reactions involving hydrazoic acid in the neat or concentrated form should be run remotely or in specially constructed bunkers. But all reactions making or involving hydrazoic acid require special precautions in reactor design and personal protection.

Hydrazoic acid is usually formed by the reaction of azide salts with acids. Hydrazoic acid is a weak acid with a pKa of 4.6 (*6*). Therefore, hydrazoic acid will form whenever any azide salt is dissolved in neutral water. For example, a 1 M solution of sodium azide in water at pH 7 will contain hydrazoic acid. Hydrazoic acid is quite soluble in water and strong acids, but it will partition into organic solvents, such as dichloromethane and ether, with a ratio of about 5:1 in favor of aqueous layer. Thus, it is possible to accidentally isolate and concentrate hydrazoic acid by simple solvent extraction and fractional distillation. Industrial incidents have occurred in this manner when solvents were not washed with base to remove hydrazoic acid prior to distillation.

Hydrazoic acid has a boiling point of 37 °C (*5*) and a high vapor pressure at room temperature leading to its high volatility. This means that hydrazoic acid can distill from flasks and reactors under ambient conditions and collect in locations such as the low spots and elbows in the overhead equipment of reactors or rotary evaporators.

General properties for hydrazoic acid are available in published MSDSs but data is often incomplete because its dangerous properties make it difficult to test. Thus, MSDSs should be taken as a starting point for azide handling and not a definitive document for safe handling of the compound. Hydrazoic acid is a powerful explosive; even as a concentrated aqueous solution it can be similar in energy to modern military explosives. The explosive limit in solvents, including water, is approximately 15% (*7*), and over 10% in the gas phase (*8*). Surprisingly, certain reactions, such as the cycloaddition of azide to form tetrazoles, are routinely run at higher concentrations. (*9*, *10*). While clearly most of such reactions do not explode, the safety of each system should be studied individually.

Some reports suggest that hydrazoic acid is relatively insensitive to initiation to explode, comparable to nitromethane (*1*, *5*). But other reports suggest it is highly sensitive and may spontaneously decompose on standing (*7*). While it is not clear why the reports differ, it is likely small variations (e.g. impurities, material of construction, concentration) may be responsible for the differences in sensitivity for specific lots. There are examples of explosions where neat hydrazoic acid accumulated and then detonated with minimal shock, perhaps from vibrations due to the agitator or even the wind. Accordingly, hydrazoic acid should not be allowed to accumulate in any form or solution, and consideration of conditions and equipment should be completed before a reaction is run to ensure such events will not happen spontaneously.

The detection of hydrazoic acid is an important component of safety on large scale. FT-IR or NIR analysis allows for direct and continuous detection of hydrazoic acid in vapors above reactors (*11*). As a practical matter, hydrazoic acid vapor in head spaces will certainly be present during plant operations with azides, but the threat of accumulation of liquid acid represents a greater danger. When hydrazoic acid is present, it will condense beginning at 37 °C, and thus temperature monitoring during operations near this temperature may be useful for detection of hydrazoic acid condensation. Although analysis is available for hydrazoic acid, the expense and potential false negatives that may result reduce the value of process analytical technology. It is better to proceed on the assumption that in all azide reactions, hydrazoic acid is present and to take the correct precautions. Proper safety plans will ascertain that no condensed hydrazoic acid will be allowed to form or collect, the head space in reactors will be swept with nitrogen, and any hydrazoic acid vapor swept out of the reactor will be neutralized in a caustic trap.

Hydrazoic acid also presents a worker safety issue as a toxic inhalant. Fortunately, there is a warning to workers at low concentrations by its pungent obnoxious odor. It also may cause severe headaches upon exposure and any such observation should immediately lead to investigation. Workers should be protected by engineering controls and personnel protective devices to prevent exposure.

The silyl analog to hydrazoic acid, trimethylsilyl azide (TMS-azide), is often offered as a safer alternative to hydrazoic acid (*12*). Nevertheless, great care should be exercised with this material as it can readily generate hydrazoic acid under a variety of conditions. Of most significance is hydrolysis, if water enters the reactor. The use of TMS-azide is problematic as it can behave normally over many runs, and then a new impurity in the starting material may catalyze its decomposition to hydrazoic acid. A safety plan for reactions using TMS-azide should always consider the possibility of hydrazoic acid formation.

In summary, most serious accidents involving azide reactions can be attributed to inadvertent isolation of hydrazoic acid. Careful planning is required to avoid explosions .

Trap 2: Handling of Sodium Azide

Sodium azide is the most common azide reagent, existing as a white solid with the formula NaN_3. It is highly soluble in water (> 30g/100 mL at 0 °C) and decomposes above 275 °C. It is extremely toxic. The general characteristics of sodium azide are available from manufacturers' MSDS sheets (*13*). Some of its large-scale uses include the gas-forming component of automobile airbags and as preservatives in biological laboratories. It is also used in pharmaceutical manufacturing for the preparation of intermediates and active drugs. Most industrial processes uses sodium azide for the initial introduction of the azide group that will eventually become a primary amine or part of a heterocycle.

Sodium azide is supplied commercially as a free-flowing white solid which tends to agglomerate on standing to form a solid mass. When uncontained, solid sodium azide tends to form powders and dusts that drift through the air to coat surfaces. This dusting tendency allows sodium azide to penetrate air-handling equipment and other locales where it may contact heavy metals such as lead and copper to form shock-sensitive explosives. Thus, a second trap occurs when sodium azide comes in contact with metals or metal salts during plant operations, usually leading to the formation of unstable and sensitive metal azides. The most common problems occur from coating of lead-containing drains and copper-containing electric wires in switches or hood motors which may lead to ignition or explosion during maintenance or repairs. Even the metal of common explosion-proof bung wrenches can react with sodium azide dust to form coatings of sensitive metal azides. When dropped, the wrenches then become a source of ignition compromising the explosion-proof rating of a plant.

Sodium azide which has fused into a solid mass is best disposed of as hazardous solid considering the low cost of the salt. Mechanical grinders or blenders should never be used. Sodium azide decomposes by excessive heat or spark, and any method that will generate either of these should be avoided.

Most commercial sodium azide is prepared by the "Wislicenus" (*14*) process, which proceeds in two steps from ammonia, sodium and nitrous oxide. The method of preparation may be important to obtaining a free-flowing solid. The addition of a compatible anti-caking agent can be useful in preventing agglomeration of the azide.

$$2\ Na + 2\ NH_3 \rightarrow 2\ NaNH_2 + H_2$$

$$2\ NaNH_2 + N_2O \rightarrow NaN_3 + NaOH + NH_3$$

Unlike other metal azides and hydrazoic acid, sodium azide itself is not considered an explosive. Sodium azide has relatively low energy in the decomposition reaction to the elements, meaning no combustion and relatively little heat are generated. Since large amounts of nitrogen are formed, the expansion of the nitrogen if unconfined offsets the heat generated, thus making it useful in airbags. The decomposition reaction of sodium azide yields sodium metal and nitrogen:

$$NaN_3 \rightarrow Na + 3/2\ N_2$$

In using or storing sodium azide, decomposition of large amounts should be avoided. The decomposition of sodium azide can be initiated by an explosive initiator, high temperature, a spark or a flame. Upon decomposition, sodium metal is formed, thus in the event of a fire, water fire suppression equipment should not be used. The sodium formed will react violently with the water, as well as generate hydrogen, an explosion hazard.

Sodium azide is not compatible with any acid as it reacts to form hydrazoic acid on contact. Even weak acids such as acetic acid will produce low levels of hydrazoic acid. Furthermore, acidified solutions of sodium azide in water may be detonable. The contact of concentrated acids on solid sodium azide will form gaseous hydrazoic acid and may explode. Lewis acids, such as zinc chloride, are acidic in water and will react with sodium azide to give hydrazoic acid. Tetrazole-forming reactions often employ Lewis acid catalysts, and reactions containing these materials should accordingly be treated as hydrazoic acid reactions if water is present.

It is important to isolate sodium azide-contaminated wastes from all other chemical wastes. These contaminated wastes must be kept basic until chemically destroyed (abated) and not allowed to contact acids or metals. Thus, it is a poor idea to mix azide wastes into general waste storage containers since a variety of compounds may be combined that could lead to dangerous situations.

The presence of sodium azide may be analyzed by titration (*1*) or ion chromatography (*15*). The analyst needs to take the same safety precautions as listed above, particularly for the disposal of analytical samples.

The list of incompatible metals not approved for direct contact with sodium azide includes all heavy metals, such as mercury, silver and lead, as well as alloys containing copper, magnesium or aluminum. Cadmium and zinc coatings are acceptable as long as the coatings remain intact and shield the potentially reactive metals that may exist at the core. Sodium azide is prepared in stainless steel reactors so iron itself is generally not a problem when dry. Other salts of azides are to be avoided because most inorganic salts, including lithium azide, potassium azide, calcium azide, and all transition metal azides, are unstable and may explode when shocked or heated.

Trap 3: Low Molecular Weight Organic Azides

Low molecular weight organic azides are often dangerous as the "ballast" of the rest of the molecule does not sufficiently dilute the energy that can be generated per gram. Any organic azide where the weight attributable to the azide group exceeds 25% of the molecular weight should be viewed with caution (*1*). Low molecular weight acyl and small aromatic azides are often sensitive to heat or friction.

A particular but little appreciated problem of low MW organic azides arises from using dichloromethane. Azide ion displaces chloride ion from dichloromethane surprisingly rapidly to form diazidomethane, an explosive material. Even an experienced chemist conducting azide chemistry might not see a problem using dichloromethane during the workup. Unlike hydrazoic acid, diazidomethane and other organic azides cannot be removed by basic washes and have been the source of several laboratory rotary evaporator explosions (*16*). In large-scale azide reactions, even 0.1% residual dichloromethane in the starting materials can produce substantial amounts of dangerous organic azides in the waste and product streams. Therefore, solvents containing displaceable groups should be used with care in azide reactions. Even for product extractions, dichloromethane is not recommended until all the free azide has been abated. In general, reactions that can potentially produce poly-azido compounds must be avoided (*17*). A particular danger is the presence of phase transfer reagents which increase the rate of azide displacement when conducted in dichloromethane and are likely to produce large quantities of diazidomethane (*18*).

$$CH_2Cl_2 + {}^{-}N_3 \rightarrow CH_2(N_3)_2$$

Many other low molecular weight azides are potentially dangerous and should be handled in solution. For example, several imidazol-1-sulfonylazide salts show a typical pattern of high sensitivity, which can be moderated by dilution with heavier counter ions or solvents (*19*). Organic azides such as acyl azides or aromatic azides such as phenyl azide are problematic. For example 4-azidobenzaldehyde has sensitivity similar to the military explosive TNT (*20*).

Each organic azide must be tested individually for a proper safety protocol (*3*). While molecular weight is one guide, compounds such as methanesulfonyl azide can be quite sensitive whereas polymers of 3,3-bis(azidomethyl)oxetane are not. It is prudent to assume all organic azides could cause problems until their safety is established (*21*). Although most organic azides are not considered dangerous in dilute solution, care should be taken to prevent azide-containing precipitates from forming due to evaporation, lowering of the solution's temperature or salting out effects. Even highly explosive azides like tetra(azidomethyl)methane are relatively safe in dilute solution. Needless to say, solutions still have to be monitored. In one incident, the concentration of solvent was allowed to increase to a level where the compound crystallized out of solution. The mixture exploded when fresh solvent was added in an attempt to redissolve the compound. The safety properties of organic azides should be fully understood before isolation is attempted at scale.

Many incidents involving azides can be attributed to one of the listed three traps. Typically, hazard analysis focuses on the reaction. Although a firm understanding of reaction kinetics and thermochemistry is required, using azides safely often involves operations that occur outside of the reactor itself. The common factor for safe processing is sodium azide containment to avoid contact with workers or incompatible materials such as metals or acids. Small changes in feed stock or equipment after the reaction has been run uneventfully many times can cause problems when unappreciated new situations arise. Thus, containment, change control and training are requirements. Life-cycle analysis is suggested to ensure that containment is guaranteed and that all unused azide is destroyed at the end of the campaign.

Life-Cycle Management of Azide

Most industrial operations involving azides begin with sodium azide. It is recommended that a life-cycle approach to safety analysis be adopted such that all azides are controlled from the moment these materials enter the gate until they are used up, shipped out or destroyed by abatement. A cradle-to-grave approach for an ordinary inorganic compound may seem superfluous but ultimately saves time, money and probably lives.

Hazard Identification, Training, and Communication

The single most important aspect of the operation of an azide facility is operational control. This requires proper managerial control, a disciplined and well-trained workforce, and a robust change control culture. Before beginning azide operations, managers should identify and maintain a list of all azide-containing materials to be used; review the manufacturer's Material Safety Data Sheets (MSDS) or other informational sources; and consult with appropriate facility safety staff and emergency personnel. Health hazard information and other safety information should be communicated to employees who work with azide materials. Applicable regulations concerning the use of azides, personnel handling of these materials and environmental requirements should be consulted. It is useful to keep a list of all the documentation associated with azide work handy so that nothing is overlooked.

All azide operations should be treated as hazardous. This requires regular training of all employees regarding the hazards and precautions for handling azides. The goal of the training should be to develop a safe attitude towards working with azides while understanding the potential hazards involved, learning the correct skills to perform azide reactions safely and preparing for unexpected hazardous conditions. It is important to treat sodium azide as a highly hazardous material and to schedule frequent refresher courses to retrain employees involved with its use and storage to fight complacency. A good schedule is to aim for yearly training if azide chemistry is ongoing.

Azide storage facilities should be clearly marked and segregated from facilities where people are working, tank farms and waste treatment areas. Buildings should indicate with signs and warning lights when azide processes are in operation. Although reactions can be run in a multi-purpose facility, it is a good idea not to run other types of reactions simultaneously with azide operations. Ideally, if a facility is dedicated to azide work, it is best not to introduce new chemistry until it is clear the facility will not be further used for azide work in the foreseeable future. It is safer to complete all azide chemistry and do a proper cleaning rather than returning to it at irregular intervals.

A process hazard analysis (*22*) should be performed at the beginning of any azide chemistry project. A "worst-case" scenario or "what if" process is the basis for a hazard analysis in which sensitivity of the materials, quantities, number of personnel potentially affected and impact on other operations should be studied. This analysis is often done by a team consisting of an engineer, an operator and a chemist. Standard corporate polices as to HAZOP, FMEA or other safety protocols should be followed and the hazard analysis should be formally documented. Process hazard analysis should be updated and revalidated at least every three years or immediately when significant changes (*e.g.*, new equipment, modified process) occur.

Toxicity Hazards and Medical Oversight

Sodium azide is highly toxic with an LD_{50} variously reported from 27 to 50 mg/kg for rats (*13*). The potential consequences of azide poisoning can be similar to some of the deadliest poisons: sodium cyanide or sodium arsenate. Exposure to azides can occur when one ingests contaminated food or water or inhales the dust or gas. Although sodium azide is not readily absorbed through the skin when dry, it is highly soluble in water (including perspiration) and then becomes a concern for skin absorption. Aqueous solutions of sodium azide form significant amounts of hydrazoic acid which is probably the greater danger since it will penetrate the skin. When spills or contact with azide occur, water for washing should be adjusted to pH >9 to minimize the hydrazoic acid content in the solution.

A typical symptom (*23*) of sodium azide exposure is a headache lasting two to four hours. Hydrazoic acid exposure may also be felt as pressure or sensation in the back of the head over longer periods of time. Other symptoms include a drop in blood pressure, dilation of pupils, bloodshot eyes, rapid pulse, nausea, and vomiting. However, lower levels of exposure may not elicit any these responses, thus any one is a signal to consider treatment. Exposure to a large amount of sodium azide by any route may cause more serious health effects, including convulsions, low blood pressure, loss of consciousness, and in the extreme, respiratory failure leading to death. First-responders should be made aware of the storage of azide (including waste storage) and have a plan in case of a spill or emergency. They should also be aware that the victim may be contaminated with azide as it could expose the emergency worker to danger. In case of a fire, fire-fighters must be informed of the presence of azide solids, solutions or waste to avoid exposing them to the danger of azide toxicity or detonation. Ideally, fire chiefs will be aware of where azide is stored, used and processed, and the expected amounts as a prudent safety practice.

In the event of ingestion, sodium azide will react with stomach acids to generate hydrazoic acid. Therefore, inducing vomiting or giving fluids to drink is not recommended. Direct CPR should not be used as the person giving CPR will be exposed to hydrazoic acid. Treatment for azide exposure will depend on the severity of the poisoning. For minor cases, workers should be removed to a safe area with time to recover in fresh air. Symptoms may be relieved with a shower, clean clothing, stimulants like caffeine, and food. Exposed employees should not be left alone until treatment is complete. In all cases, victims should be kept under medical attention until the exposed individuals recover completely.

Reaction to exposure may be worse when it occurs on an empty stomach, and employees are encouraged to eat before the start of their shift. Any employees showing signs of exposure must be removed immediately from the process area, and their blood pressure monitored hourly until it is clear there is no concern for exposure. In all cases of poisoning, medical help should be obtained rather than treating the exposure based on information in this chapter. There is no antidote to azide poisoning, but fatalities are extremely rare. Although sodium azide is in wide-spread use in automobile airbags, the azide is contained and there have been no reports of poisoning from airbags.

Special personnel training and procedures should be in place in the event that someone ingests sodium azide. Because sodium azide is acidified by stomach acid, the contents of the stomach will contain highly toxic hydrazoic acid. In the event that vomiting has occurred, personnel should isolate the stomach contents and neutralize them with basic water if possible. Any substance containing sodium azide (including food, water or vomit) must be collected and sent for abatement.

Once the symptoms of exposure have dissipated, and a doctor finds no lingering effects, employees can return to normal duties. There is currently no medical evidence that exposure to hydrazoic acid or sodium azide causes chronic illness. Employees who are exposed, or think they may have been exposed, should follow the Center for Disease Control guidelines (*23*).

Persons involved routinely in azide operations should be monitored by medical staff. A common effect of azide poisoning is low blood pressure. The use of blood pressure monitoring devices in common areas is suggested to encourage self-examination in case of concern.

In the event of symptoms of exposure, there should be a formal incident report and investigation into the source of exposure. Then one must examine procedures and personnel protection equipment to see if modifications are required. Another process hazard analysis should be conducted to prevent a recurrence of the problem. Should similar incidents be repeated, senior management must take charge to understand why this is occurring and to initiate action before a serious event happens. Azides must be contained at all times, and there should be no worker exposure during normal operations.

Facilities

The danger of impact leading to azide explosions require unusual precautions in facilities. Ideally, in work environments where solid azides are handled, the floor and all hard objects within striking range of azides should be cushioned to minimize energy transference from an inadvertent impact. Plexiglas barriers where open vision lanes are important or foam insulation can be used. A procedure should be established to account for and secure hand tools that may inadvertently fall into an azide-processing operation.

Each worker's location should be monitored frequently so that assistance can be provided or aid summoned in the event of an emergency. Personnel devices that sound an alarm if the person remains stationary too long or becomes horizontal are one possibility. Electronic surveillance via security cameras also provides rapid response as long as a worker is assigned to monitor the cameras. Manufacturing areas containing azide should be controlled after the individual features of each building have been analyzed and understood. Only necessary personnel with proper training should be present and the presence of each worker should be documented.

In the case of reactions capable of generating hydrazoic acid in high concentration, the operations should be conducted remotely with barriers, warning lights and other engineering controls to prevent entry during hazardous operations.

Ideally, facilities that will handle azide in any manner are best designed for the continuous presence of azide at all times. Such an "azide-proof" facility would be housed in an enclosed azide-resistant area that provides for solid, liquid and vapor azide containment. This allows the best design to be incorporated rather than requiring compromises to be rigged later in non-dedicated facilities. For instance, a design that allows the entire interior surface of a reaction bay to be hosed down is a useful means to prevent azide dust from remaining on otherwise difficult-to-clean surfaces. Provisions for inert gas tracing of conduits containing copper wires and removal of metal bearings are also useful. The use of tracing requires oxygen sensors and breathing air for worker protection. Co-location of dedicated scrubbers with reactors and dedicated make-up rooms to allow contained introduction of azide into the reactor are preferred. Air-handlers should be fitted with filters and scrubbers to prevent azide from reacting in vents or motors. The ability to run reactions remotely is always preferred when working with azide. While few companies have large-scale equipment designed for dedicated azide work, a conscientious team of workers and management will be able to devise a work plan that still allows processing under safe conditions

Personal Protective Equipment (PPE) and Devices

The first thoughts for safe azide work start with facilities and training; however, personal protective equipment provides what should be redundant protection. Provision should be made to launder and disinfect protective garments and devices. This is especially important for equipment worn about the face where inhaling chemical dust or contact with mucous membranes can happen. Coveralls may be washed in a laundry without special consideration so long as the garments are not heavily contaminated. For small amounts of azide contamination, treatment of wash waters from a laundry is not necessary as cleaning solutions are typically basic. However, all water wastes generated within the plant from the cleaning of any equipment, personnel or clothing must be collected and sent for abatement.

Each operation should be analyzed to determine appropriate personnel protection. This is, of course, in addition to the protective equipment that may be required for typical plant hazards, such as hard hats, safety shoes, etc. For sodium azide, this would include rubber boots, cotton coveralls or coats, gloves, safety glasses and face shields. Coveralls should not have cuffs or ridges where solid sodium azide may collect. The coveralls should not have metallic fasteners that can react to form metal azides. Antistatic outer garments and footwear should be used. If direct contact with sodium azide or hydrazoic acid is expected, a Tyvek respirator hood, leather gloves and breathing air or respirators are recommended. After contact, operators should shower and don clean coveralls. A small amount of sodium azide on coveralls is not considered a hazard so long as it remains dry. Therefore, removal of the soiled coveralls before the workers wash up is a necessary consideration.

Footwear should be rinsed before leaving the operations area and the waters collected and sent for abatement. In the event of localized contamination, washing with water buffered to pH 9 is recommended. When contact with sodium azide is expected to continue for a protracted period, operators should use only air-supplied respirators as the multi-gas/acid vapor cartridges break down quickly and could expose the user to hydrazoic acid fumes.

We have not spoken of personal protection against azide explosions since any significant threat of a serious azide explosion should automatically bar the presence of workers. If there is such a situation, processing must be conducted remotely. In small reactions such as found in laboratories, use of blast shields and heavy leather gloves in addition to regular safety equipment is recommended.

Proper protection of operators and other personnel present in azide handling facilities requires preparation, thought, well-trained personnel and the use of proper personal protective equipment. If a situation arises where explosions or serious contamination may occur, then processing must be conducted remotely. Preventive measures should be implemented to curtail danger to personnel. Short-changing this safety measure can end in regret.

Transportation and Handling of Azide to and within the Facility

Generally sodium azide is shipped by truck without unusual precautions to the plant location in 25 to 50 kg plastic bags inside fiberboard drums. The density of sodium azide is high (1.84 g/cc) so the containers are relatively small. Sodium azide has been given UN number 1687, Class 6.1 (toxic material). Care should be taken during transportation to avoid excessive heat, fire or electrostatic discharge (ESD). Sodium azide can be moved about the plant using standard trucks or forklifts with the usual care taken to secure the containers on the pallets to avoid spills. In the event of damage to a fiberboard container releasing sodium azide, the spill must be cleaned up by a HAZMAT team and sent for abatement.

Sodium azide should not be allowed to become wet for both quality issues and the danger of forming hydrazoic acid. For most operations, the plastic bags are sufficient to protect the sodium azide, however, the fiberboard containers should be protected from rain or water. Sodium azide which has become contaminated by water, metals or either inorganic or organic materials should not be used. Contaminated material may be returned to the vendor or sent for abatement. The presence of foreign substances in sodium azide may make the material more hazardous, and such material should be treated carefully after consideration of the specific impurities.

Generally, sodium azide is accepted on certificates of analysis (CoA) from vendors (usually of 95 to 105 wgt %). If analysis is required, the container must be sampled in a special sampling room prepared for handling azide. Such a facility should have the same characteristics as a plant designed for azide use, including special hoods, drains and personnel protective devices.

Sampling and weighing of azides are not recommended in storage areas or in general-purpose sampling or weighing rooms. Because of its dusting characteristics and the increased chance of spillage, sodium azide sampling and weighing require special controls. Samples of sodium azide should be sent to analytical labs in specially designated or specially marked sample containers. Analytical procedures have been performed by colorimetric analysis, nitrogen evolution, and FT-IR or ion chromatography. All samples sent for analysis and wastes from the analysis procedures should be collected and properly abated following analysis. If samples are to be archived, they should be saved in special storage containers isolated from other materials.

Storage Facilities

Due to the danger of an explosion or decomposition, sodium azide should be stored in dedicated facilities. The storage buildings should not be made of metal or contain metal shelving, and should have blow-out walls or roofs to avoid over-pressurization in the event of azide decomposition in case of a fire. Incompatible materials should not be present. The storage facility construction should protect against sodium azide becoming wet under all weather conditions. The building should not have water-based fire suppression equipment. Adequate ventilation is required to prevent accumulation of azide vapors. The maximum safe temperature for sodium azide storage has not been reported; however, sodium azide in automobile airbags is routinely subjected to temperatures above 40 °C suggesting that cooling is only required for the most extreme temperatures found at industrial sites.

Operators who maintain the azide storage facility or transport azide should be trained in azide handling and on specific aspects of the work at the facility, depending upon their assignment. Special care in operating forklifts is required to prevent damage to sodium azide containers. So long as the integrity of the sodium azide containers is not compromised, no special personnel protective equipment is required. Sodium azide containers should never be opened in the storage areas.

In general, storage facilities do not absolutely require special construction or maintenance to be viable for azide storage. However, the immediate vicinity should be free of metals, water and other incompatible materials to avoid possible decomposition and/or explosion. There may, therefore, be advantages to designing a dedicated facility for azide storage and handling.

Weighing

Sodium azide should be obtained from vendors in containers and sizes appropriate to the batch size in the plant to avoid difficulties in weighing azide. Ideally, pre-packaged quantities targeted for exactly the charge required will significantly reduce hazards related to weighing out samples, storage of opened containers and staging. In such cases, it may be best to accept the lot based on CoA rather than sample for analytical clearance. If partial containers are to be used, special weighing rooms should be used similar to the sampling rooms described above. The unused portion must be carefully resealed to avoid contact with incompatible materials or water, but in consideration of the relatively low cost of NaN3 and the problems that can occur upon exposure to moisture, perhaps disposal of unused small quantities is more cost effective and safer.

In the event that sodium azide is repackaged after weighing, only compatible plastic containers should be used. Care must be taken to avoid contamination, and the new containers must be marked with the appropriate labels and safety data.

Laboratory and Testing Operations

Because the quantities of azide used in laboratories are small, employees may think of them as insignificant in regards to safety (*16*). Unfortunately, azide dust and metal azides will build up over time to cause explosions in pipes and hoods during maintenance operations and at other unexpected times. The requirements for the use of azides in a laboratory setting should be nearly identical to those found elsewhere in the facility. But since most laboratories employ open electrical equipment and unprotected hoods, extra vigilance is required. Further, because abatement is time-consuming, azide-containing wastes are typically poured into laboratory sinks. In analytical labs associated with plants and in hospitals where azide is used as an anti-bacterial, accidents are common because of this practice which allows azide to react with the metals in drains.

For R&D labs, analytical chemists in particular should be trained in handling azides since their training does not typically emphasize the hazards of compounds like azides. Reactions involving azide should be enclosed and connected to caustic water solution scrubbers in order to trap any hydrazoic acid vapor or azide dusts, similar to the procedures used in the plant. All wastes from lab experiments should be collected separately from other laboratory wastes, labeled appropriately, and abated. All unused azide samples and azide contaminated materials in analytical labs must be collected and properly abated.

Production Equipment

Two approaches to azide-compliant facilities have been used: azide-proof and azide-resistant. Azide-proof means the plant is safe for azide use because all potentially incompatible materials have been removed, and equipment is isolated, remotely run and designed for azide use. These facilities are very safe but very expensive and over-designed for non-azide chemistry in the future. The more common approach is to make the facility azide-resistant, providing protection only for the equipment expected to come into contact with azide. Since the rest of the building is not protected, engineering and operational disciplines are required to prevent unexpected contamination.

Most azide reactions are run in multi-purpose plants. Those involving concentrated hydrazoic acid generally require isolation in bunkers and remote control because of the danger of explosions, but not many reactions call for this reagent. Reactions in which hydrazoic acid is generated *in situ* in dilute solution and reacted without isolation, such as tetrazole forming reactions, are often conducted in multi-purpose facilities. Safety hazards analysis should be carefully performed to assure the facilities are appropriate to the chemistry being conducted. Ideally, all azide reactions would be conducted in a separate building, similar to the requirement for hydrogenations that take into account the possibility of a large explosion due to gaseous reagents.

If it is necessary to use general purpose facilities, the reactors should be positioned in a segregated and shielded area, preferably close to windows or blow-out walls and away from other operations or personnel areas (break rooms, changing areas, etc). Where possible, a partition wall (panels) is recommended to direct the potential blast towards the outside so as to reduce the effect on other equipment. Activity should be avoided that may trap operators in the area between the reactor and the plant wall. Only employees who have been properly trained and are necessary to the work should be admitted to the area.

Equipment must not contain incompatible materials such as copper or copper alloys, lead, and aluminum. If bearings or exposed wire could come in contact with sodium azide, compatible coatings, nitrogen tracing or other strategies should be used to avoid direct contact. All reactions or isolations involving azides should be in enclosed systems.

Sodium azide should not be stored or staged in process buildings for longer than necessary to complete the operation. Hazards analysis of the quantities to be stored should be undertaken to assure the quantities do not exceed acceptable risks. When on the production floor, sodium azide in fiberboard containers should be isolated from other incompatible materials and protected from water. The use of glass-lined equipment is recommended for most azide applications. In some cases, stainless steel can be used but its compatibility with the reaction mixture must be determined before its use since iron azide is detonable in the dry form. Stability of azide-containing products should be tested for stability to iron azide (if stainless steel will be present) and other Lewis acids.

The reactor top (head) should have minimum piping, with the fewest bends and loops in order to prevent accumulation or holdup of liquid hydrazoic acid. Hydrazoic acid is a highly volatile liquid that may evaporate easily and recondense in pipes due to relatively small temperature differentials. Piping found in a multi-purpose environment that is not required for the azide reaction should be dismantled or dead-headed.

A condenser should be installed above the reactor in a vertical position on the vent riser pipe (closest to the reactor top) to prevent any liquid hydrazoic acid from escaping into the overhead piping. Where reactions are run under reflux, conditions should be used to avoid fractionation of the hydrazoic acid from the solvent. Temperature monitors should be installed in the pipes before and above the condenser. The presence of hydrazoic acid distillate can be inferred by a temperature reading of 37 °C corresponding to the boiling point of hydrazoic acid. An indication of accumulating hydrazoic acid should lead to immediate emergency procedures to shut down the reaction and evacuate the area until the status of the chemistry can be ascertained.

Where it is impractical to avoid metal surfaces or parts, encasement of units, such as closets or glove boxes, with Plexiglas or other coatings is recommended. PVC shrink-wrap coatings or dipped/sprayed epoxy paints are acceptable but should be routinely inspected for cracks or breaks in the surfaces where metal may be exposed to azide dusts.

Vent sizing for reactors should be engineered based on the stability data from the individual reaction mixtures.

A highly reliable automated heating/cooling system should be provided for the reactor jacket. Hot water circulation may be preferred to live steam in some reactions where the azide product may be thermally unstable and accumulate on walls above the reaction mixture. For certain reactions, hazardous conditions may result if a hole in the reactor jacket allows water into the reaction mixture. Where water is not compatible with the reaction mixture and the results of a leak would be catastrophic, non-aqueous heating and cooling media should be used. Maintaining a dry atmosphere in the reactor is always recommended. A method to detect the presence of water, whether from failure of the condenser cooling system or from undetected pitting of the reactor lining, is recommended.

A nitrogen purge system should be available to eliminate azide fumes from the reactor before it is opened and to assure no hydrazoic acid remains in the system.

Reaction mixtures should be transferred from one reactor to another by gravity flow through Teflon-coated pipes containing no holdups or low points. Pumping, when required, should not use gear pumps if solid sodium azide is present. Piping integrity should be verified periodically.

A dedicated scrubber containing water at pH >9 should be connected to all reactors containing azide. The scrubber should be located as close as possible to the reactors, and the vents connecting the reactor and the scrubber must have no bends or low spots where hydrazoic acid may accumulate. The vent lines and scrubber ideally should be made of plastic or glass. A pH monitoring device is recommended to assure that the caustic is not exhausted during processing. The scrubbers must be dedicated so that azide vapors cannot find their way into other non-azide process equipment. During filtration or another isolation processes, the equipment should be contained and vented to azide scrubbers. If air handlers are used, the air should not be directly vented to the atmosphere and the air handlers should be azide-compatible.

Introduction of sodium azide into the reactors should be contained, either through glove boxes or separate isolation rooms. Ideally, a glove box attached to a reactor port can be used. The glove box or other equipment for introducing azide should be constructed from antistatic or non-metallic materials. The inside of the box should be kept under negative pressure. The box can be charged with bags of azide, closed and the reactor port opened. Introduction of one bag of azide at a time is desirable. If sodium azide is to be placed into reactors directly through hatches, provision should be made to contain spills and to clean the hatch area to avoid the retention of sodium azide within the hatch assembly. Alternatively, if solid addition is not practical, sodium azide can be slurried or dissolved in a separate room and pumped into the reactors. Gear pumps are not recommended: gravity feed is the safest.

Nitrogen inertization is not mandatory if the reactor does not contain flammable solvents. All equipment should be cleaned and dried after each batch.

Because of the possibility of azide vapors or dust, air handlers should be protected from contamination by the use of filters or in-line scrubbers to prevent azide contamination of motors or wiring. Nitrogen tracing of electrical wiring or analytical sensors may be necessary in some cases.

The rationale for the design of production equipment is the same as that for designing facilities: it is best to consider azide use before fabrication so that the equipment is constructed correctly from the start rather than requiring modification afterwards. The more typical situation is the utilization of multi-functional equipment; for this, careful consideration is needed before processing starts.

Cleaning

Facilities containing azides should be kept clean and orderly to simplify detection of azide spills or other potentially hazardous conditions. Azide dust should not be allowed to accumulate on structural members, heating coils, utility lines, equipment, or electrical fixtures. A regular cleaning program for facility interiors should be in place to prevent the accumulation of azide dust and waste. In buildings containing azide, floors should be cleaned with basic water wherever practical. Small spills should be swept up or dissolved in basic water. Reaction bays with rounded corners that can be entirely hosed down reduce the chances of azide dusts accumulating in odd places.

It is recommended that when mopping floors or wiping up spills with wet rags, the water be buffered with potassium hydroxide, sodium carbonate, or trisodium phosphate to a pH of 9. Non-abrasive sweeping compounds that are compatible with the azides may be used when water is not practical. During azide decontamination, activities involving large volumes of organic solvents (generally over 1L), should be prohibited.

Cleaning protocols are more efficient and more easily implemented if cleaning needs were taken into account during the design phase of a facility. Failing that, extra care is needed during cleaning to maintain a safe operation.

Decontamination and Waste Collection

Azide-contaminated waste should be isolated from other plant wastes at all times to prevent catalytic interactions that could lead to violent decomposition or the formation of explosive metal azides. Process streams, cleaning solutions, containers, scrubber solutions and any materials in contact with azide must be treated to destroy the azide. Allowing azide-contaminated wastes to mix with other plant wastes may create explosive or toxic mixtures, including metal azides and hydrazoic acid. Since azides are routinely used to stop bacterial growth, introduction of azide wastes into the waste treatment facility without prior abatement may negatively affect the bacteria being used to treat the waste, even at parts per million concentrations. Compromised bio-remediation facilities are very expensive to recover.

During the design phase, plants operating azide processes should be fitted with dedicated drains in which spills, waste waters and cleaning solutions can be contained and separated from other plant wastes. This is very expensive to incorporate into an existing plant. The pH of the waters in the drains should be monitored to remain basic. Drains should be emptied and cleaned after azide operations are complete and all liquids captured by the drains should be sent for abatement. Employees involved in cleaning, decontamination or abatement should have proper personnel protective equipment as detailed earlier.

Hydrazoic acid will partition (dissolve) into organic solvents. Cleaning solvents such as acetone and methanol used for washing reactors should be treated as azide-contaminated unless shown otherwise.

If azide solids or solutions have come into contact with metals, chemical decontamination may be required. For water-insoluble heavy metal azides, such as copper or lead, treatment with acid solutions of sodium nitrite will be required to dissolve and neutralize the azides. Solid azide spills should be swept up before the area is washed with basic water and sent for abatement.

Sodium azide-contaminated packing materials may be washed to remove the azide component and disposed of in the normal trash. The washes from packing materials, however, should be sent to abatement. The wash waters for clothing, rags or other cleaning equipment may be disposed of normally if the azide contamination is minor. Cleaned clothing and towels can then be reused after normal washing. Alternatively, azide-contaminated boxes, bags or cloths may be burned without washing.

Sodium azide is often shipped in fiberboard containers, double sealed in plastic bags. These materials should be burned without cleaning and not reused. Because the fiberboard container comes from an azide-contaminated factory, it should be considered azide-contaminated. The plastic bags can be washed and the washing solutions sent for abatement, or placed in uncontaminated bags and sent for incineration.

Azide wastes should be isolated, clearly marked and the pH should be adjusted to >9. They should not be stored for extended time periods. If such storage is unavoidable, the pH of the waste should be monitored, and the waste should be protected from evaporation and concentration. Azide waste will often generate gases so waste containers should be vented and the emitted gases safely handled. Lab-scale waste containers may be stored in the back of a hood. Larger containers will need a dedicated venting system.

The collected wastes should be transported to the azide abatement facility regularly and treated as soon as feasible thereafter. Transportation should be in plastic containers or tanks made of or coated with compatible materials. All containers should be properly marked as hazardous azide-containing wastes. All azides must be destroyed chemically or by incineration and never commingled with other plant wastes.

The complexity of waste handling and treatment can approach that of the use of azides in production, but the associated hazards render such attention a good idea. Failure to assign sufficient importance to the handling of waste can result in incidents years or even decades after azide processes are discontinued.

Abatement

Inorganic azides and hydrazoic acid are abated by the reaction of an oxidizing agent under acidic conditions. Because acidic conditions produce hydrazoic acid, the order in which the reagents are added is critical, and the oxidizing agent must be added to the azide wastes before the acid is introduced. Sodium azide content in aqueous wastes should be at a concentration of 5% or less for safe abatement.

The standard procedure for abating water-soluble inorganic azides (*1*) is to add sodium nitrite (oxidizing reagent) and then add acids such as formic, acetic, hydrochloric or sulfuric. As the acid is added, large amounts of gases, including nitrogen, nitric oxide, nitrogen dioxide and other oxides of nitrogen, are evolved.

$$\boxed{\begin{array}{c} NaNO_2 + HCl \rightarrow HNO_2 + NaCl \\ \\ HNO_2 + NaN_3 \rightarrow N_2 + NO + NOx \end{array}}$$

The amount of sodium nitrite must be sufficient to oxidize all of the azide present. Because the intermediate nitrous acid is unstable, some of the sodium nitrite will be lost to auto-decomposition. It is necessary, therefore, to have excess nitrite present.

When the evolution of nitrogen and nitrogen oxides is complete, the acidic solution should be tested to assure that excess nitrite (or other oxidizing reagent) is still present to ensure that unreacted azide is no longer present. A simple test is starch-iodide paper: a blue color indicates nitrite is still present when the azide decomposition is complete. Once the azide is completely reacted, the acidity should be neutralized prior to discharge. The choice of acids depends on cost, materials used in construction of the abatement facility and ultimate waste handling of the spent solutions. Slower, more controlled reactions occur with weak acids such as acetic acid or formic acid.

Sodium nitrite is in general use because of its low cost and safety, but it has the unfortunate property of generating large amounts of gaseous nitric oxide. Abatement of the resulting nitric oxide then becomes a problem. Some nitric oxide can be abated by reaction with air, but because nitrogen dioxide reacts with water to make more nitric oxide, simple water scrubbers are not sufficient (*24*). Oxidation of nitric oxide is an issue that requires a catalytic scrubber if the quantities involved exceed air pollution standards.

Abatement procedures require acid treatment and are usually done in glass-lined reactors fitted with efficient stirrers. Because of the large quantities of gases evolved during abatement, the reactors should be oversized. The top of the reactor is fitted with a condenser and attached to a scrubbing column made of plastic or glass with glass or ceramic saddles. The scrubber is fixed for a counter-flow of basic water to be pumped from the bottom vessel to the top of the tower and then allowed to flow back to the vessel by gravity.

The waste azide solutions are pumped into the reactor and diluted if necessary to approximately 5% azide content. Solid sodium nitrite can be added before or after the azide solution is added. An acid solution can be pumped or gravity fed slowly to control gas evolution so that the gases do not cause unreacted azide wastes to leave the reactor. At the end of the abatement, the reactor is checked for the presence of excess nitrite or other oxidizing reagent. The solution is then neutralized and sent to waste treatment as non-hazardous waste.

Many organic azides are potentially explosive, but since they are not water soluble, the acid oxidizer abatement used for inorganic azides cannot be used. Instead, most water insoluble organic azides can be destroyed by reduction with hydrogen, triphenylphosphine or by incineration. For small amounts of material, solutions of triphenylphosphine in organic solvents will rapidly convert azides into imines with the evolution of nitrogen. Further treatment with water will produce amino compounds and triphenylphosphine oxide, which in most cases can be disposed with normal organic wastes.

Recycling and Reuse of Solvents Used in Azide Chemistry

Because hydrazoic acid will dissolve in both water and organic solvents, care must be taken when recycling solvents used in azide-containing processes. Washing organic solvents prior to distillation with basic water and subsequent analysis to ensure the absence of azide are recommended. If hydrazoic acid is present in spent solvents, subsequent distillation during purification may inadvertently separate this low-boiling component and concentrate it. The opposite problem exists for non-volatile azides as they will concentrate in the reactor during distillation. Azide-containing waste should not be distilled to avoid potential safety hazards. Distillations involving azide-contaminated materials should be carefully monitored but in consideration of the cost required to monitor and avoid hazardous situations, solvent recovery is only cost effective for unusual cases.

Maintenance and Repair

Maintenance operations involving major repairs, changes, or the use of hazardous equipment should not be performed when azides are present. An approval procedure should be established to ensure that the area has been inspected for azides and is safe for the desired work. When approved, only required and authorized maintenance or construction operators should be present during these repairs.. Records should be maintained for inspection, repair, and servicing of process and handling equipment.

For equipment that may have been exposed to azides during operations, special procedures should be developed for maintenance. Opening bearings that may contain copper-containing alloys or electrical boxes containing copper wires should be done with extra care and personnel protection. Similar care should be used in waste plumbing lines if the presence of metal azides is suspected.

In cases where inspection, visual or other, shows the likely presence of metal azide contamination, the equipment should be decontaminated prior to maintenance or repair. Heavy metal azides are generally not soluble in water alone, so chemical decontamination with nitrite and acid solutions may be required. Such treatment may degrade the equipment beyond reclamation, thus prevention of contamination of the equipment is always a better idea. No repair or maintenance of hoods, plumbing or electrical equipment used in azide processes should be undertaken while flammable organic vapors are present.

Glass-lined reactors should be inspected for pitting that may cause iron or water to be introduced into the reaction mixture. If stainless steel is used, the reactor and associated equipment should be inspected for stability to the reaction mixture. A broken metal stirrer or other metal debris striking solid sodium azide within a reactor could cause a problem.

Emergency Controls and Considerations

Azide operations should be designated with recognizable signs. Although no standards currently exist for signage, placards showing both explosion and toxic dangers are suggested. Plants in operation should be closed to employees who lack training in azide work. Worker exposure to azide should be reported immediately to the plant health official and will nearly always require the attention of properly trained medical personnel. Please refer to the section on response to employee exposure to azides.

Failure of equipment which releases azide-contaminated materials should be treated as serious events. Personnel in the plant and surrounding area should be evacuated, and HAZMAT teams with Tyvek suits and self-contained breathing air should be sent to clean up the spill. In the event of gaseous hydrazoic acid release, emergency procedures and evacuation of the entire plant may be necessary. Plant personnel must be knowledgeable about local, state and federal requirements for responding to emergencies, and reporting releases and spills.

For failures not involving escape of azide-containing materials, reactors should be cooled to stabilize azides in solution and prevent concentration of hydrazoic acid or azides. Most azides dissolved in cool dilute solutions will be stable for long periods (assuming precipitation of solids azides does not occur) and reactions may be continued after the equipment is repaired or abated as required.

Conclusion

Azide chemistry is useful synthetically and is characterized by high yields and clean reactions. The azide molecule allows results that cannot easily be attained by alternative chemistry. Industrially it is limited by issues of explosivity of some intermediates. Most companies will actively seek alternative routes to azide use to avoid the extensive safety issues required for safe processing. However, in the case of some compounds such as AZT, where the final product contains the azido group, or for drugs containing tetrazole groups, there are no alternatives to the use of azide. Azide has been used on industrial scale by pharmaceutical companies and by contract manufacturers who specialize in understanding the risks. There are a number of companies with extensive experience in azide reactions, and these companies have an excellent safety record. This experience has shown that azide reactions can be safe on industrial scale.

Still, azide processing must be taken seriously. Problems, including fatalities, have occurred. Most incidents result from failure to contain azide or from unwarranted changes to procedures. The problems generally come months or years after a process has been running successfully. Communication and training of operators and research staff is necessary so that they understand the implications of changes to the process. Operational discipline is required, and change control is critical.

This chapter has tried to highlight some of the issues and strategies to cope with azide chemistry. As with any general topic, anyone engaging in azide chemistry is advised to verify that the suggestions presented are relevant to their processing and facilities. It is hoped that during the process development and safety analysis, as much time will be spent on issues arising from outside the reactor as on the reaction chemistry inside it. The risks can be understood and controlled through a combination of planning, safety awareness, engineering and plain good sense.

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Chapter 4

Chemical Reaction Safety in the Research Laboratory − Where It All Begins

Stephen M. Stefanick[*]

Janssen Pharmaceutical Research and Development LLC,
1000 Route 202 South, Raritan, New Jersey 08869
[*]E-mail: SSTEFANI@its.jnj.com

The primary focus of this chapter is to address "chemical reaction safety" in the early research and development chemistry laboratory and manage potentially hazardous reactions. Typically at this early R&D stage the scientist's goal is to make the target compound by using whatever chemistry is available from the literature or their own synthetic knowledge and expertise, and at times, this chemistry can be potentially dangerous. This chapter discusses and highlights several strategies, approaches and tools that the early R&D chemist can apply to gain a better understanding of the potential chemical reaction safety issues associated with performing chemical reactions even at very small scales.

"I didn't see any temperature rise when I ran the reaction". "The reaction only foamed a little bit when I ran it". "The sample turned only slightly brown when I dried it in the warm vacuum oven."

Introduction

These are representative comments a bench chemist might say when carrying out chemical reactions and isolating organic compounds in the small scale discovery research laboratory. In this chapter, attention on developing proper strategies to recognize, observe and even quantitate potential chemical reaction hazards and provide strategies to avoid potential chemical hazards in the early

In Managing Hazardous Reactions and Compounds in Process Chemistry; Pesti, et al.;

chemical research environment will be discussed. Many excellent references, books, strategies and programs are abundant throughout the literature (*1*) that address the concept of “process safety” as it pertains to reaction scale up, pilot plant and manufacturing. However, the typical small scale chemical reserach laboratory is a very different environment compared to large scale chemical miniplants, pilot plants and manufacturing facilities, and each presents its own series of challenges to safely conduct work. Hidden dangers exist in the research lab and accidents can be catastrophic even on a small scale.

At this stage of research, often times very little consideration and regard is paid with respect to the types of chemicals used in the synthesis of such small batches of drug candidate or the ease of applicability to perform the reaction on larger reaction scales. Equipment concerns such as reaction flask size, cooling / heating requirements and even reaction time are not pertinent at this stage. However, chemical reactions carried out even under these very small reaction scales have potential chemical reaction hazards that can surface and possibly result in an accident or injury. Hence, there is a need for a distinction to be made between the concepts of “process safety” in the process chemistry / manufacturing arena and “chemical reaction safety” in the relatively smaller chemistry research laboratory. Although there may be some similarity and concepts may overlap between the small scale chemical research laboratory versus the large scale manufacturing facility, different strategies, approaches and thinking are required to address the chemical reaction safety concerns on the small scale. Several tools that may be used to identify situations/substances where the energy from the raw materials or reaction itself will not be safely absorbed by the reaction environment will be presented throughout this chapter. Learning tools to promote awareness about what key information is available to help identify chemical reactivity hazards in the research laboratory will also be discussed.

Discussion

The Different Types of Hazards

To address potential chemical reaction hazards in the small scale research laboratory, the scientist should first recognize that there are several types of reaction hazards. Hazards can be classified as into three categories: the chemical hazards, the reaction/rate hazards, and mechanical/operational hazards (Figure 1).

Each hazard type offers its own set of challenges to identify, control and / or eliminate. Assessment strategies to help identify the potential for chemical reaction hazards should focus on all three areas to help establish a basis of safety allowing the scientist to perform a particular chemical reaction safely without incident.

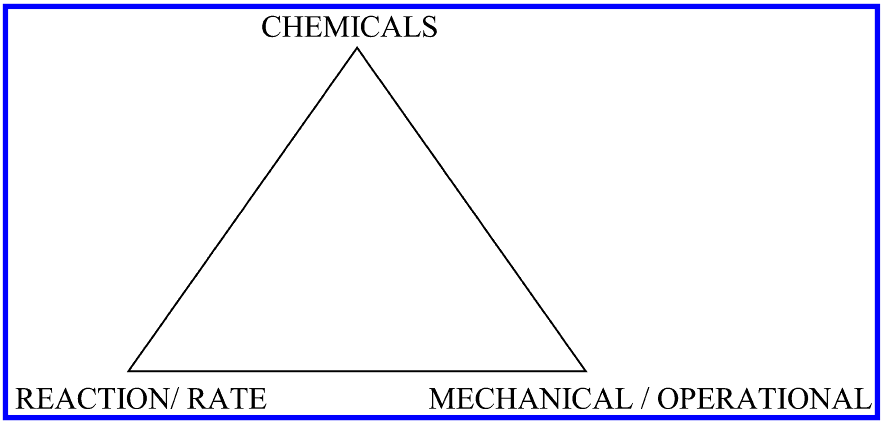


Figure 1. Hazard Categories

Chemical Hazards

During the focus on the chemicals, the lab scientist should recognize that all the chemical compounds, solvents and reagents that will be utilized in a particular chemical reaction should be evaluated for potential chemical reaction hazards. A thorough literature search should be the primary starting point to any chemical reaction hazard evaluation strategy. A good starting point for such information is typically the Material Safety Data Sheet (MSDS). The scientist should take the time to look up each MSDS for all the chemicals being utilized and examine the pertinent sections, especially those pertaining to stability, reactivity and incompatibility to gain an understanding about the characteristics of each material being used. The scientist should also examine the reaction and balance the chemical equations under evaluation to account for all reaction products, off-gasses, and potential by products that are included or may be generated in the particular chemical reaction. With the use of automated chemistry drawing and modeling programs, balancing the entire equation is frequently overlooked but such an exercise will provide important clues as to whether a potential reaction hazard may exist from the reaction itself or a reaction by-product.

Next, the scientist should identify and recognize if there is a particularly dangerous chemical functionality present in the compounds being reacted. One’s academic chemistry training, scientific knowledge, and experience should lead to the recognition that certain chemical functionalities have the potential to be hazardous either energetically or as toxic agents. Carbon-carbon and carbon-nitrogen triple bonds, nitro groups, diazo groups, epoxides and perchlorates are all highly energetic compound functionalities that can lead to potential chemical hazards. Examples of these and other such highly reactive functional groups are listed in Table 1 as well as in the literature (*2*).

Table 1. Examples of Highly Reactive Functional Groups

C-C and C-N triple bonds and metal salts (acetylenic compounds)
Adjacent N-O atoms (nitro, nitroso compounds)
Adjacent and consecutive O-O pairs (peroxides)
Adjacent and consecutive N-N compounds (diazo compounds)
Adjacent C atoms bridged by O or N (epoxides)
O-X pairs (perchlorates)
N-metal pairs

Listings of highly energetic compounds with sensitive chemical functionality, significant reactivity, and peroxide forming structures are widely available in the literature (*3*, *4*). The lab scientists should gather as much general information about the reactivity of starting materials, solvents, products and by-products of any particular chemical reaction that will be considered. The chemist should also examine if any of the reaction solvents are peroxide forming (Table 2). Many chemists are unaware that otherwise common lab solvents such as alcohols have led to explosions from peroxide build-up.

Peroxides present or generated during a chemical reaction or subsequent disposal of a spent reaction mixture represent a serious potential hazard. Measures should be taken to first prevent their presence or formation, and then eliminate or minimize the hazard. Once all the literature information is collected, a decision on whether additional reaction safety testing is needed can be addressed. Sometimes there is the option of considering parallel routes to a key intermediate and safety aspects may drive the decision which chemistry is tried.

Reaction / Rate Hazards

A consequence of attempting to address chemical reaction hazards at an early stage of research is that the scientist may not have true knowledge or understanding of how much heat may be generated by the chemical reaction, whether the reaction mixture decomposes during reaction or workup, or if any raw materials or products are unstable or shock sensitive. To gain an understanding of the potential reaction / rate hazards associated with a particular chemical reaction, chemists should answer questions regarding the use and generation of thermally unstable reagents, mixtures and reaction products before carrying out the reaction. Based on this understanding, proper precautions, engineering controls and personal protective equipment can be implemented if required. It’s prudent at this stage to check for chemical incompatibilities for the combination of materials used in the chemical reaction. The reactivity of binary mixtures can even be estimated from several on-line databases (*6*, *7*) before actually performing the reaction in the lab.

Table 2. Typical Examples of Peroxide Forming Solvents (*5*)[a]

Acetaladehyde
Acrylaldehyde
Allyl ethel ether
1-Allyloxy-2,3-epoxypropane
Bis(2-ethoxyethyl) ether
Bis-(2-methoxyethyl) ether
1,3-Butadiene
1,3-Butadiyne
2-Butanol
Buten-3-yne
Butyl ethyl ether
Butyl vinyl ether
2-Chloro-1,3-butadiene
Chloroethylene
2-Chloroethyl vinyl ether
Cinnamaldehyde
Crotonaldehyde
Cyclopropyl methyl ether
Diallyl ether
Dibenzyl ether
Dibutyl ether
1,1-Diethoxyethane
1,2-Diethoxyethane
3,3-Diethoxypropene
Diethyl ether
Diethylketene
2,3-Dihydrofuran
Diisopropyl ether
1,1-Dimethoxyethane
1,2-Diethoxyethane
3,3-Diethoxypropene
1,3-Dioxane
1,4-Dioxane
1,3-Dioxol-4-en-2-one
Dipropyl ether
Di(2-propynyl) ether
Divinyl ether
2-Ethoxyethanol
1-Ethoxy-2-propyne
2-Ethylacrylaldehyde oxime
2-Ethylbutanal
2-Ethylhexanal
Ethyl isopropyl ether
Ethyl propenyl ether
Ethyl vinyl ether
2-Furaldehyde
Furan
2,4-Hexadien-2yn-1-ol
2,5-Hexenal
2-Indanecarboxaldehyde
2-Isopropylacrylaldehyde
Isobutyraldehyde
Isopropyl vinyl ether
Isovaleraldehyde
Limonene
1,5-p-Menthadiene
Methoxy-1,3,5,7-cyclooctatetraene
2-Methoxyethanol
2-Methoxyethyl vinyl ether
4-Methyl-2-pentanone
2-(1-Methylheptyl)-4,6-dinitrophenyl crotonate
2-3-Methyl-2-methylenebutanal
2-Methyltetrahydrofuran
Methyl vinyl ether
Alpha-Pentylcinnamaldehyde
Propionaldehyde
Sodium 5,8,11,14-eicosatetraenoate
Sodium ethoxyacetylide
1,1,2,3-Tetrachloro-1,3-butadiene
Tetrahydrofuran

[a] Data extracted from reference (*5*), Desert Research Institute Webpage http://www.dri.edu/images/stories/editors/ehs/ehsdocs/Lab_Safety_PEROXIDE_forming_compounds_2005.pdf.

Early drug discovery and development scientists should be aware that certain reaction categories can be very exothermic. Heats of reaction values for typical organic reactions are listed in Table 3. Appropriate measures to control the heat generated should be taken when performing highly exothermic reactions, even on small to moderate scales. A base-line knowledge and appreciation of the chemistry to be run and expertise how to handle reaction temperature control are required to perform these reaction types from the very small lab scale to very large manufacturing scale.

The scientist should make a determination whether the reaction in question is exothermic where boiling, reflux and the production of off-gasses in either a controlled or uncontrolled manner is critical to carrying out the reaction safely in the lab. Even the smallest temperature rise observed in a common glass round-bottomed reaction flasks can be an indication that a possible uncontrollable chemical reaction will occur as the reaction is scaled up to moderately larger quantities. A basic understanding of how much heat is generated during a particular chemical reaction and what would happen if loss of cooling occurred is fundamental for carrying out chemical reactions safely in the lab.

Table 3. Examples of Typical Heat of Reaction Values (*8*)[a]

Estimated Energy Release during chemical reaction	*Chemical Reaction type and Energy released*
0-50 kJ = Weak 50-100 kJ = Medium 150-300 kJ = Strong 300 kJ = Very Strong	Bromination reaction: < 50 kJ/mole Friedel-Crafts reaction: 53 kJ/mole Typical Acid/Base Neutralization: 56 kJ/mole Epoxidation reaction: 96 kJ/mole Amination reaction: 120 kJ/mole Nitration reaction: 130 kJ/mole $NaBH_4$ Reduction: 150 kJ/mole Oxidation reaction: 300 kJ/mole Grignard reaction: 400 kJ/mole Hydrogenation of a NO_2 group: 560 kJ/mole

[a] Data from reference (*8*). Copyright 2008, Wiley-VCH.

Hence the need to appreciate and recognize that different lab vessels of variable capacities have quite a different ability to transfer and dissipate any reaction heat to an external cooling environment. Typical heat removal capacities for variable reaction vessels required to remove a moderate reaction energy of 30 watts/liter of energy are included in Table 4. A certain knowledge of appreciating heat removal capacities and expertise is required to perform exothermic reactions on the larger lab, kilo lab, pilot plant and manufacturing scales, but the same care and attention should be applied even at much smaller reaction scales. What the scientist may consider a small temperature rise in the lab may not be as small as the reaction scale increases where heat removal capacity of the reaction vessel plays a more significant role in the control and outcome of the reaction.

Table 4. Typical Heat Removal Capacities for Various Sized Reaction Vessels (*9*)[a]

Reactor Example	***Estimated Heat Transfer Coefficient U***	***Estimated ΔT required to cool 30 watts/liter***
500 mL round bottom flask	200 W/m^2K	2°C
RC-1 1 L SV01 reactor	150 W/m^2K	5°C
50 gallon mini-plant reactor	250 W/m^2K	16°C
250 gallon plant reactor	250 W/m^2K	26°C
1600 gallon plant reactor	250 W/m^2K	44°C

[a] Data from reference (*9*). Copyright (1993) Gulf Professional Publishing.

Therefore, the need exists to develop an understanding of chemical reaction hazards, heats of reaction, and the thermal instability of the chemicals routinely used in synthesis. These issues should be addressed while at small scale because ignorance of these factors can easily result in injury even at small scale and the problem may not be as easily rectified as reaction scales increase.

Also not typically considered are issues about the reaction profile that include whether the reaction is carried out as a batch versus semi batch reaction. A batch reaction is typically defined when starting materials are added essentially all at once and the reaction then initiates. A semi-batch reaction is one where some of the starting materials are added to the reaction at the onset and the key raw material / reagent is added in a controlled manner over time. Other reaction rate issues that need consideration could include:

- Determination of the solvent role and whether concentration influences the reaction rate.
- Determination of role of reaction temperature and whether the starting reaction temperature is too low which may result in accumulation of unreacted starting materials.
- Determination of whether the reaction can be catalyzed by the equipment's materials of construction (if not performed in glassware).
- Determination of the potential effect of impurities that may be present in different batches of starting materials purchased from different vendors on reaction rate and/or initiating undesired side reactions.

A thorough evaluation of the anticipated chemical reaction behavior with respect to all of these reaction/rate considerations adds a level of understanding and confidence that the reaction can be run safely even before conducting chemistry.

All these issues need to be addressed prior to actually performing the chemical reaction even on a small scale for a proper safety mindset. A fundamental understanding of the "safe reaction space" versus operating outside the safe limits where thermal decomposition and uncontrolled reactions can occur, should be discussed prior to actually carrying out the lab experiment.

There are two "worst-case temperature rise" situations that may arise during the reaction. The first situation arises during the normal operating reaction limits when the heat of reaction from the desired chemistry becomes uncontrolled due to loss of cooling or stirring and results in an adiabatic temperature rise of the reaction. The second situation builds from the first and results from unwanted chemistry that occurs during loss of reaction control and may result in the adiabatic decomposition of an unstable reactant or product (Figure 2). Knowledge of these fundamental situations is essential to reaction safety and needs to be determined and addressed prior to starting a chemical reaction.

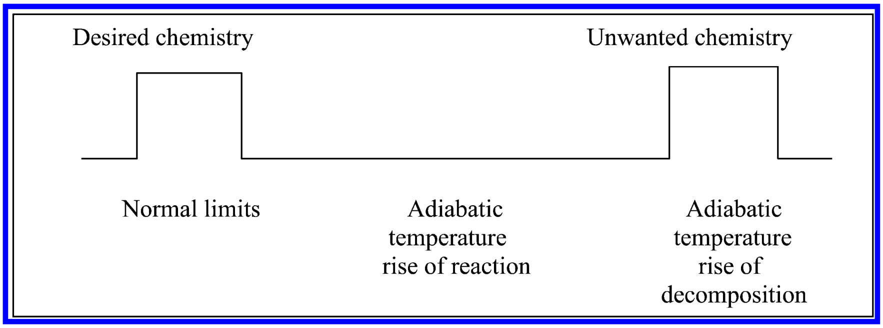


Figure 2. Factors affecting desired vs. undesired chemistry

Scientists have powerful analytical tools to screen and perform reaction safety testing using specialized instrumentation. Commonly available tools include differential scanning calorimetry (DSC), accelerating rate calorimetry (ARC), the Advanced Reactive System Screening tool (ARSST) and reaction calorimetry. Such instrumental tools are routinely used to gain an understanding of thermal stability of the reaction materials, the heat of the chemical reaction and the worst-case adiabatic temperature rise if something goes wrong while running the reaction. The theory, operation and methodology for each of these and other chemical hazard testing instruments can be found elsewhere and will not be discussed in detail here. However, these three instrumental techniques can easily be utilized to provide a basic understanding and screening of any potential chemical reaction hazard associated with either the chemicals being used or with the chemical reaction itself.

For example, DSC is a valuable instrumental tool to quickly evaluate the thermal stability of the chemicals used in a reaction and to determine the proper procedures for handling, drying and storage for each. DSC is also used to test reaction mixtures and products for potentially hazardous chemical reactions and decompositions (*10*). The DSC is considered a rapid screening tool. The information resulting from DSC screening should only be considered an estimation of the chemical hazard potential and never as an absolute guarantee of a safe situation. The DSC test requires only milligram sample sizes for testing and is usually run over a very broad temperature range that would be inclusive of all temperatures the reaction could attain. However, if testing the actual chemical reaction that is not a complete solution, one can never be sure if the sample pulled from a heterogenous reaction mixture is truly representative of the entire reaction. Routine DSC offers no pressure data collection. However, the resulting DSC data and interpretation should be followed up by more thorough testing if a potential chemical reaction hazard is identified.

ARC is another instrumental test method that typically provides useful information regarding the reaction parameters. Typical sample sizes are in the 3-5 g range and with the proper ARC instrument setup, mixing can be achieved and pressure data collected. The ARC results provide an assessment of the runaway potential of a chemical reaction and/or the thermal stability of a chemical compound or mixture under increasing temperature conditions. The ARC test thus provides critical information to better define temperature and pressure ranges for the chemical reaction to support running the chemical reaction at larger reaction scales.

Other useful tools in the calorimetry arsenal are the EZMax, OptiMax, and the RC1 reaction calorimeter produced by Mettler-Toledo AutoChem. When properly equipped, these heat measuring instruments are lab scale reaction calorimeters that are routinely used to screen, measure and observe the heat of reaction behavior of chemical reactions on a small scale. Performing a reaction in one of these calorimetric instruments allows the scientist to gain an understanding of how much heat is generated under the tested reaction conditons. The energy being released by the chemical reaction in the form of heat is directly proportional to the rate of the chemical reaction and hence reaction calorimetry can be used to study reaction behavior and kinetics. This rate of heat release is typically referred to as heat flow and is very easily measured by the reaction calorimeter.

This quantitiative measure of reaction heat (heat flow) can then result in appreciation of the reaction behavior to determine if the reactor to be used for a larger reaction will be capable to safely remove the generated reaction heat. The reaction calorimetry results may indicate if it is best to run the reaction in a batch or semi-batch modes. Reaction calorimetry would also signify if any accumulation of unreacted starting materials was occurring as the reaction progressed if it was not recording heat generated during the addition. Additionally reaction calorimetry can give an estimation of the quantity of heat and worst-case temperature rise that could result from the loss of reaction control.

Examples of how such instrumentation and testing can help identify potential chemical reaction / rate hazards will be presented later in this chapter.

Mechanical or Operational Hazards

Mechanical or operational hazards arising from the type of equipment selected by the research chemist will also affect the safety of the chemical reaction and a determination of whether the potential for fire or explosion exists. Consequences arising from using electric heating mantles, overhead electric stirrers, water baths, etc. should be carefully evaluated since they can all have drastic effects on safety if not chosen properly. For example, heating mantles and overhead electric stirrer motors may generate electrical sparks that can potentially cause highly flammable solvents to ignite or explode. The use of an ice-water bath may not be the proper choice for reaction cooling when using a water-reactive reagent such as alkyl lithiums or reactive metals. This may lead to a fire if the glassware breaks due to a stress fracture or an accident. Liquid transfer in tubing or transfer lines may result in the static buildup of a charge that could potentially ignite flammable solvents or reactants. Many other examples of hazardous situations can be listed for an ordinary laboratory.

The lack of mechanical or operational knowledge will affect the outcome and safety of chemical reactions on the small lab scale. It is important to understand the proper temperature control issues such as the effect of loss of cooling or a runaway reaction that could result in excessive heat generation and subsequent spewing of reaction contents out of the vessel. Simple issues such as placement of the temperature measurement probe in an incorrect position that can produce inaccurate measurements may occur. Other issues that are not frequently considered include the effect of inadequate stirring, the addition of the wrong amounts of chemicals or their addition at the wrong rate or in the wrong order, any situation that may lead to leaks from the reactor jacket or reflux condensers, and finally human factors and scientist error. All these issues, although seemingly minor, can have a drastic impact on performing the chemical reaction safely.

Strategies that could be implemented and adapted as standard operating procedures for the scientist to consider may include something as simple as a reaction safety review. Usually scientists are more prone to think the reaction safety review is for larger reaction scales. However, recognition that surprisingly violent explosions can happen even at the small reaction scales. This small-scale reaction safety review may consist of a “mini-hazard and operability study (HAZOP)”, a mini “what-if checklist” or even something as simple as an informal yet documented discussion among scientists addressing what chemistry is being performed. Such a discussion about how the reaction will be conducted would be a valuable exercise to document the potential chemical and mechanical reaction hazards associated with running a particular reaction on a small scale. Such documentation would serve as a valuable resource in case the particular reaction is ever scaled up to larger quantities. In particular, such a small-scale reaction safety review would be invaluable to conduct at the university level where small scale chemistry is usually run and new scientists unfamiliar with laboratory hazards will be entering the laboratory.

Issues To Consider in Running Safe Small Scale Chemistry

Some type of reaction safety discussion should occur routinely among all the lab scientists involved to address a particular chemical reaction, particularly if the chemical reaction is something new or novel. Such discussions could be carried out informally either in person, teleconference, or e-mail and a summary of the identified issues should be documented. Examples of discussion topics may include a review of the “mechanics” of the procedure and how a particular reaction will be carried out in the lab, for instance:

- All available data from material safety data sheets (MSDS) or other literature or online databases
- Details about what equipment is being used to carry out the reaction (glassware, fixed reactor system, material of construction, etc.)
- How will the reaction temperature be regulated? Will a heating mantle, oil bath, ice-water, etc. be used to control temperature?
- How will the temperature and pressure be monitored?
- The methodology to monitor the reaction.
- Reaction work-up considerations (extraction, rotary evaporation, filtration).

- Product isolation strategy and potential waste disposal issues with spent solvents that may contain peroxides or other hazardous materials.
- Personal protective equipment to be worn and other safety factors (shield, toxic agents, high flammability, etc.) to be considered.

The available thermal testing data from DSC, ARC and reaction calorimeters can be discussed to reach a consensus on whether the available reaction safety information is adequate to safety perform the chemical reaction or if additional safety testing will be required.

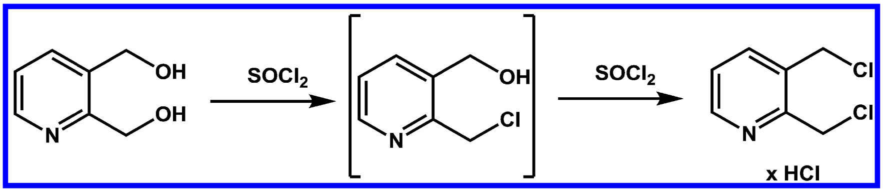
During the race to make viable drug candidates as quickly as possible, scientists may frequently overlook chemical reaction safety issues. In today's environment where early drug discovery groups are preparing larger quantities of materials to support early toxicology and other studies to support project acceleration, reaction safety issues like those discussed above become even more important. The goal becomes to prevent potential reaction hazards as the early researcher works to prepare kilogram amounts of materials rather than the smaller amounts they are typically accustomed to synthesizing. One should view a reaction safety testing program as a means of gaining an understanding of the potential chemical reaction hazards associated with exothermic reactions to prevent accidental releases of toxic materials, destruction of equipment and facilities, injury to people, and potential harm to neighboring communities. The overall program strategy should focus on testing chemical reactions for potential hazards, screening chemical raw materials for thermal instability, conducting safety evaluations prior to reaction scale-up, and relying on in-house experience for similar reactions. Evaluation of the potential chemical, reaction and mechanical hazards allow the researcher to feel more confident that the reaction can be run successfully without incident.

To this point we have discussed factors for a basic appreciation, understanding and acceptance for safety testing for chemical reaction hazards. The following examples demonstrate how reaction calorimetry plays a vital role in identifying potential chemical reaction hazards during the preparation of drug substances during discovery and early development research.

Examples of Safe Chemistry in the Small Scale Chemistry Lab

2,3-Bis(chloromethyl)pyridine is an intermediate used to prepare a former drug candidate at Johnson & Johnson (*11*) and illustrates how the RC1 reaction calorimeter was used to identify a critical reaction parameter (Scheme 1).

The reaction conditions initially developed and forwarded to the chemistry team were carried out using neat thionyl chloride as both reactant and solvent. Several issues were observed on the small reaction scale that presented challenges for running the reaction on larger scale. Initial lab scale observations revealed that the reaction was very exothermic with vigorous sulfur dioxide off gassing and had the potential to lose control and run away even on small reaction scales.



Scheme 1. Preparation of 2,3-bis(chloromethyl)pyridine. Reproduced with permission from reference (11). Copyright (2002) American Chemical Society

Based on the small scale lab experience, the original reaction conditions using neat thionyl chloride were not amenable to scale up with available reactor equipment. After performing a mini-hazop discussion to address the potential chemical reaction hazard, additional chemical reaction safety testing using the RC1 reaction calorimeter was recommended to gain a better understanding of the reaction profile. The reaction calorimetry work employed the use of semi-batch conditions. The reactor was charged with the raw materials and solvent and then followed by a number of iterations of a controlled addition of thionyl chloride to maintain the desired reaction temperature with minimal and controlled offgassing.

It is important to understand how much heat energy is generated during the particular chemical reaction. The energy being released by the chemical reaction in the form of heat is directly proportional to the rate of the chemical reaction and hence reaction calorimetry can be used to study reaction behavior and the kinetics of the reaction. This rate of heat release is typically referred to as heat flow and is very easily measured and graphically displayed by the reaction calorimeter software program.

Careful analysis of the resulting heat flow curves (Figures 3 and 4) for the multiple experiments led to the eventual recognition that a change is reaction conditions was required because the resulting heat flow curves were not “feed controlled” and thus not controllable in relation to the rate of thionyl chloride addition.

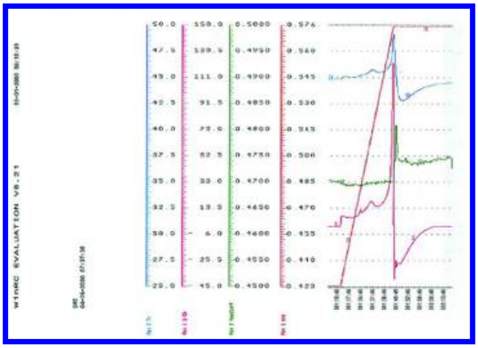


Figure 3. RC-1 Heat Flow Curve for Experiment in MTBE at 45°C. Blue = Reaction temperature; Tr Red = Heat flow; Green = Reactor pressure; Orange = $SOCl_2$ addition. Reproduced with permission from reference (11). Copyright (2002) American Chemical Society (see color insert)

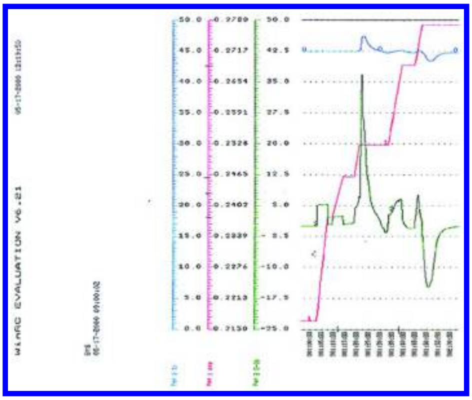


Figure 4. RC-1 Heat Flow Curve for Experiment in Toluene at 45°C. Blue = Reaction temperature Tr; Red = $SOCl_2$ addition; Green = Heat flow. Reproduced with permission from reference (11). Copyright (2002) American Chemical Society (see color insert)

For example, the red heat flow curve in Figure 3 indicated that the reaction was clearly not 'feed controlled'as evidenced by the '*en-masse*' exotherm after a significant amount of thionyl chloride had accumulated in the reactor. This accumulated thionyl chloride then reacted spontaneously and resulted in a serious uncontrolled outgassing from the reaction mixture as shown by the green pressure curve. The outgas was tentatively identified as a mixture of sulfur dioxide, the expected by-product of the chlorination reaction and isobutylene that results from decomposition of MTBE by the HCl produced during the chlorination reaction.

In a repeat run but in toluene, the green heat flow curve in Figure 4 indicated that the reaction had not fully initiated after addition of one equivalent of thionyl chloride as illustrated by the red addition curve in Figure 4. Again, as the second equivalent of thionyl chloride was added, the reaction occurred spontaneously. The addition of thionyl chloride was again exothermic under these conditions and not 'feed controlled.'

The large volume of sulfur dioxide that was generated rapidly in an uncontrolled manner in both reaction scenarios precluded scale-up of these reaction conditions as well. A modification of the reaction conditions was required that produced a more desired semi-batch "feed-controlled" reaction profile during the addition of thionyl chloride that would allow better control of the reaction exotherm and sulfur dioxide outgassing. It was known that chlorinations of alcohols via an *in situ* generated Vilsmeier-Haack complex proceeded under mild conditions (*12*).

Calorimetric investigation using a Vilsmeier reagent for chlorination showed that the addition of the thionyl chloride was still exothermic but the resulting heat flow was now almost completely feed-controlled. This is illustrated by the parallel nature of the red heat flow curve and green thionyl chloride curve in Figure 5. The red heat flow increased as the first equivalent of thionyl chloride was added then subsided once the thionyl chloride feed was stopped midway in the reaction. The heat flow again resumed upon addition of the second equivalent of thionyl chloride and continued until reaction the addition was complete.

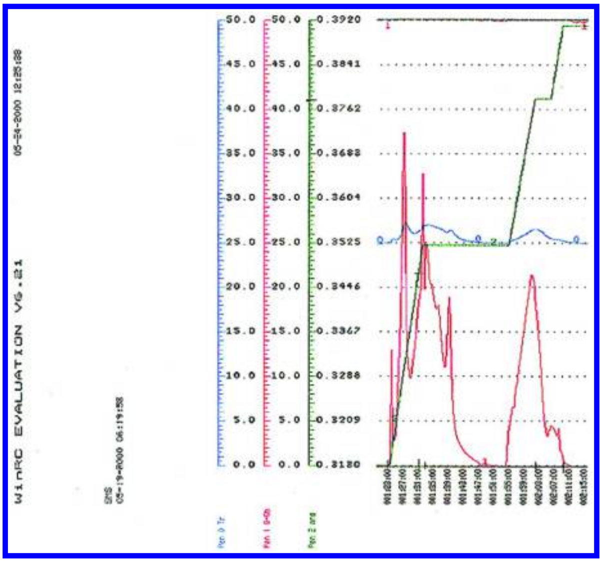


Figure 5. RC-1 Heat Flow Curve for Vilsmeier Chlorination Experiment for Toluene/DMF at 45°C. Blue = Reaction temperature Tr; Red = Heat flow; Green = $SOCl_2$ addition. Reproduced with permission from reference (11). Copyright (2002) American Chemical Society (see color insert)

Although the addition of the thionyl chloride was exothermic under these conditions, it was essentially feed controlled. The reaction was reasonably well controlled under these conditions and moderate evolution of sulfur dioxide was not seen until the second equivalent of thionyl chloride was added.

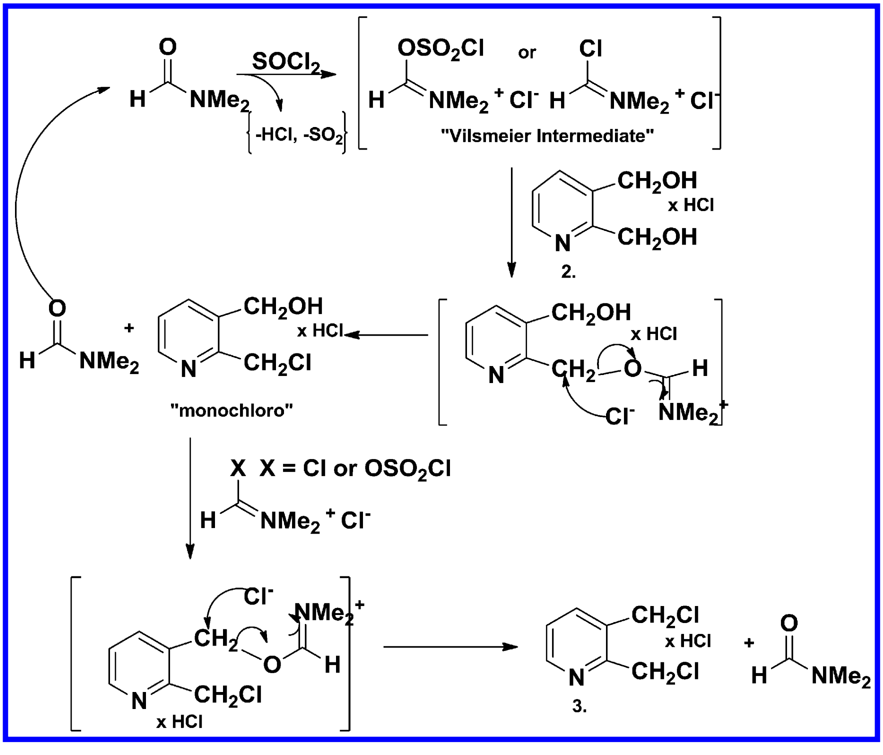
The reason the reaction was now controllable was due to the change in the reaction mechanism to reflect a Vilsmeier-type reaction wherein dimethylformamide (DMF) reacted catalytically with thionyl chloride and the intermediate was a better chlorination agent than those achieved using the neat thionyl chloride reaction conditions as illustrated by the proposed mechanism in Scheme 2.

After following the proposed reaction safety testing protocol consisting of a literature search and a mini-hazop review, performing several reaction calorimetry experiments led to an improved process and a better understanding of the reaction heat flow and reaction behavior. The final reaction conditions employed the use of toluene as a solvent, 1.2 eq of thionyl chloride added in a controlled manner, and a catalytic amount of DMF. The reaction calorimetry experiments also allowed us to optimize the reaction conditions by minimizing the amount of thionyl chloride which in turn simplified the product isolation, ameliorated the hazards, reduced raw material costs, and diminished the waste disposal problem. Recognition and consideration of the potential chemical reaction hazard at the early research stage allowed the facile and safe preparation of kilogram amounts of the material.

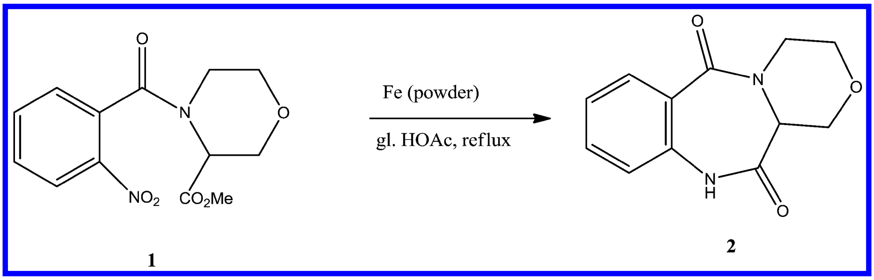
A second example (*13*) (Scheme 3) involves a reductive cyclization reaction of an aromatic nitro derivative using an iron/acetic acid combination that eventually produced kilogram amounts of the desired 1,3,4,12a-tetrahydro-11*H*-[1,4]-oxanio[3,4-c][1,4]benzodiazepine-6,12-dione (**2**).

The original reduction procedure provided to the chemistry team was not immediately amenable to scale up for several reasons:

- The reaction was run at high dilution (5% w/v) and led to very large volumes to manipulate during scale up.
- The reaction needed 6.3 equivalents of iron pellets that resulted in a significant agitation problem that are compounded as the reaction scale increased.
- The reaction required more than 20 h to complete.
- It required a laborious reaction work up and a chromatographic purification to isolate the product.
- A low yield for the reaction (62%).



Scheme 2. Modified synthesis of preparation of 2,3-bis(chloromethyl)pyridine. Reproduced with permission from reference (11). Copyright (2002) American Chemical Society



Scheme 3. Synthesis of 1,3,4,12a-tetrahydro-11H-[1,4]-oxanio[3,4-c][1,4]benzodiazepine-6,12-dione. Reproduced with permission from reference (13). Copyright (2003) American Chemical Society

Initial reaction optimization and process development work on small scale resulted in several improvements to the original reaction conditions:

- Doubling the reaction concentration to 10% (w/v).
- Reducing the iron use to only 2.5 equivalents of Fe powder.
- Reducing the reaction time to only 1.5 h.

These improvements increased the purity, simplified the reaction work up and most importantly eliminated the chromatographic purification. Moreover, these improvements resulted in a yield increase from 62% to 84% and improved product quality that was crucial for the success of the subsequent reaction steps. However, upon initial scale up to prepare larger multi-gram quantities, a safety issue regarding an uncontrollable exothermic reaction was encountered. After discussion in a mini-hazop exercise, agreement was reached that additional reaction safety and thermal stability testing was warranted.

DSC thermal screening testing of the starting material and reaction product were recommended to better understand their respective thermal stability. Testing showed that the starting nitro methyl ester **1** underwent an exothermic decomposition initiating at 176 °C, about 55 °C above the operating temperature for this reaction. It was believed that heat removal by reflux of the acetic acid reaction solvent could provide an initial barrier to a runaway reaction if the reaction heat was difficult to control upon scale up. Also, the DSC test of the product demonstrated that the benzodiazepine final product **2** was thermally stable and would not undergo a thermal decomposition even when heated up to 300 °C. Based on these results, it was concluded that if any nitro methyl ester **1** accumulated as the reaction exotherm progressed and if the solvent evaporated, the residue of the nitro methyl ester **1** could thermally decompose and compound an already hazardous situation. Therefore, it was the opinion that these reaction conditions represented a significant chemical reaction hazard due to the reaction thickening, poor stirring, large worst-case temperature rise potential and ability for the starting nitro compound to decompose energetically if accumulated. Additional RC-1 reaction calorimetry testing was required to better understand the reaction heat generation rate and potential worst-case temperature rise.

The initial reaction calorimetry experiment was carried out using the addition of powdered iron to a heated solution of nitro methyl ester **1** in acetic acid at 50 ˚C. The iron powder (325 mesh) was added portion-wise (green line) over 1 h to generate the following heat flow curve (Figure 6).

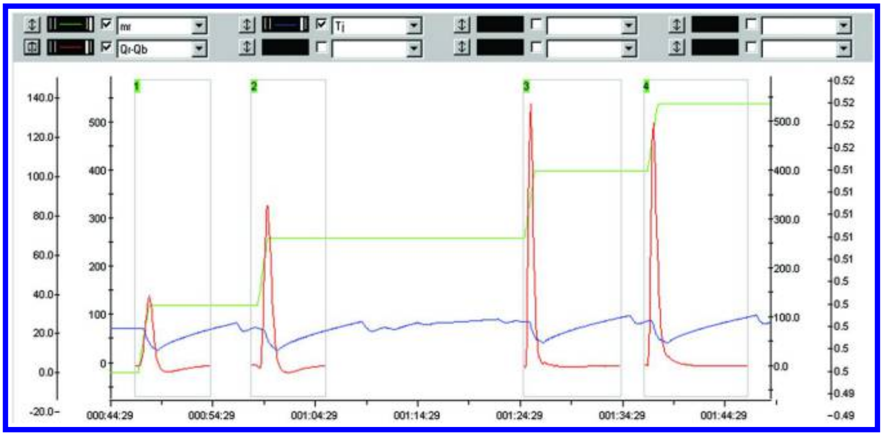


*Figure 6. RC-1 Heat Flow Curve for Portion-wise iron addition to methyl ester **1**. Red = Heat flow (y-axis in watts); Blue = Tj Jacket temperature (y-axis in °C); Green = Iron addition (y-axis in kg); (X-axis is experiment time in hours). Reproduced with permission from reference (13). Copyright (2003) American Chemical Society (see color insert)*

The resulting heat flow curve (red curve in Figure 6) suggested that each iron addition step was very exothermic under the test conditions. Thickening of the reaction mixture resulting in poor stirring again occurred as the reaction progressed. The RC-1 program calculated a very large worst-case temperature rise potential that suggested that if loss of reactor control (cooling and stirring) and full accidental mischarge of all the iron occurred, vigorous solvent reflux and ejection of the reaction mixture from the reaction vessel would likely occur. This led to the investigation of a reverse addition scenario where the starting nitro methyl ester **1** was added to a suspension of iron in acetic acid at elevated temperature.

In a second reaction calorimetry evaluation, a solution of nitro methyl ester **1** in acetic acid was added using a liquid dropping funnel with a metering stopcock over 25 min to a mixture of iron powder (325 mesh) in acetic acid at 75 °C and generated the following heat flow curve (Figure 7).

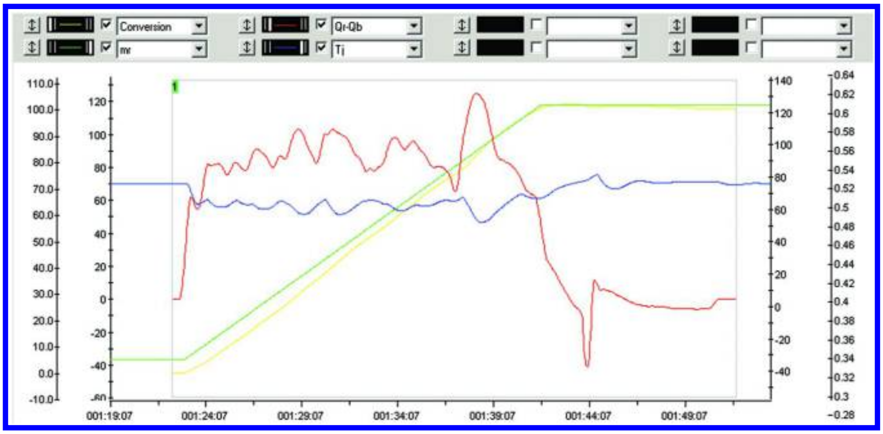


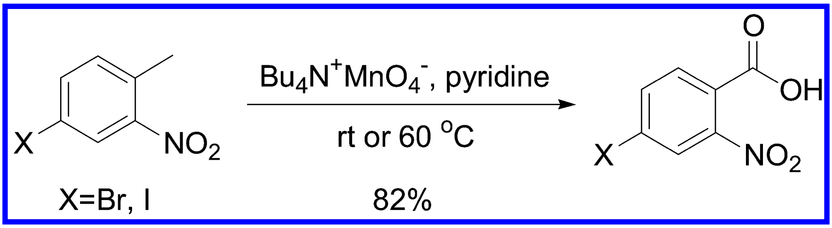
Figure 7. RC-1 Heat Flow Curve for Portion-wise controlled solution addition to Iron powder. Red = Heat flow (y-axis in watts); Blue = Tj Jacket temperature (y-axis in °C); Yellow = Thermal conversion to product (y-axis in %); Green = Starting nitro ester 1addition (y-axis in kg); (x-axis is experiment time in hours). Reproduced with permission from reference (13). Copyright (2003) American Chemical Society (see color insert)

The heat flow curve (red line) suggested that the addition of the acetic acid solution of the starting nitro ester **1** to iron is still exothermic yet is feed controlled. The rate of conversion to product based on the heat flow – referred to as the thermal conversion rate (yellow line) - nearly matched the feed rate of the acetic acid solution of the nitro methyl ester 1 (green line). No thickening or inadequate stirring was observed (*14*). Again, the reaction calorimetry results calculated a very large worst-case temperature rise potential if a mischarge of the entire acetic acid solution of the starting nitro methyl ester **1** was accidentally added all at once and that with loss of cooling and stirring in the reaction vessel, vigorous solvent reflux and spewing of the reaction mixture from the reaction vessel could occur. The caveats regarding the thermal instability of the starting nitro compound **1** were not as relevant in this instance since it is added in a semi-batch manner and would not be allowed to potentially build up to any sufficient quantity to accumulate. Also, solvent reflux would be sufficient to remove the excess heat via the reflux condenser if the reaction began to reach out of control conditions.

Despite the exothermic nature of the reaction coupled with the potential chemical reaction hazard, these RC-1 modified conditions were recommended for scale up for several reasons. The idea of a feed-controlled addition combined with the ability to meter in the solution of **1** in acetic acid was acceptable for reaction scale up for this stage of early development to meet material timing demands. As part of the engineering controls for this reaction, mechanical safeguards were implemented that included the use of metering pumps for all liquid additions to prevent full accidental mischarge of the solution of nitro methyl ester **1** that could result in a hazardous situation. No reaction thickening or stirring issues that could lead to poor heat transfer were observed using these conditions. Therefore, the reverse addition conditions offered a substantial improvement in reaction control and safety when compared to the original conditions wherein iron was added to the reaction mixture.

The use of a mini-hazop discussion led to the recognition that additional testing was needed to safely perform the reaction. DSC screening provided a basic understanding of the potential thermal stability of the starting materials and product. The reaction calorimetry evaluation at this early stage of research demonstrated that reversing the order of addition resulted in an improved reaction profile that could be more easily managed as reaction scales increased.

A final example (*15*) illustrates other chemistry that is typically performed in the early research chemistry lab. The reaction in question involved the oxidation of a 4-halo-2-nitrotoluene with tetrabutylammonium permanganate in pyridine (Scheme 4).



Scheme 4. Oxidation of 4-halo-2-nitrotoluene. Reproduced with permission from reference (15). Copyright (2006) American Chemical Society

Tetrabutylammonium permanganate (TBAP) was chosen because of its reported stability and solubility in organic solvents (*16*). Using pyridine as the solvent afforded quantitative conversion after several hours at room temperature but resulted in a reaction safety issue on a slightly larger scale. When all the reactants were mixed, the reaction possessed a variable induction period, ranging from several hours to days, before the oxidation initiated. The length of the induction period seemed to be longer at higher water levels in the reaction mixture; however this was never quantitatively determined. In addition, the oxidation reaction rate was extremely fast and vigorously exothermic once initiated, which raised the concern of a runaway reaction.

A mini-hazop discussion examined all the known facts about this reaction at that time. The discussions included that it was well known that increasing temperature typically helps to eliminate induction periods. However, because of the notorious reported instability of organic permanganates at elevated temperatures, it was concluded that more thorough chemical safety testing was needed. The thermal stability of the starting materials and the product were tested by DSC. DSC screening results showed that 4-halo-2-nitrotoluene and 4-halo-2-nitronitrobenzoic acid were stable up to 200 °C, TBAP underwent a substantial exothermic decomposition that initiated around 91 °C (Figure 8).

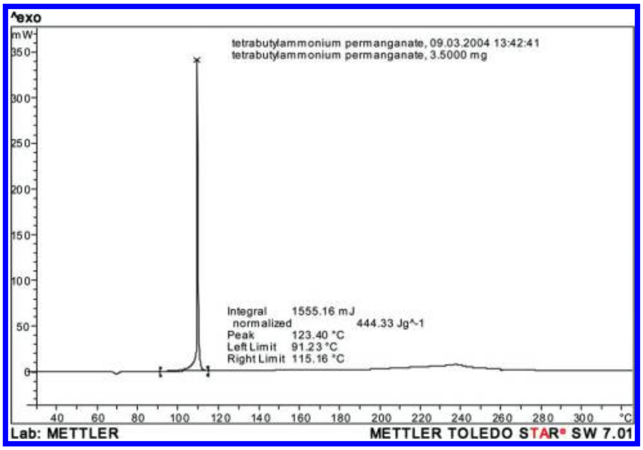


Figure 8. DSC test on TBAP. Reproduced with permission from reference (15). Copyright (2006) American Chemical Society

An ARC test was then run on a solid TBAP sample. An exothermic decomposition (Figure 9) occurred that initiated at 59 °C (lower than in the DSC test) and the self-heating rate exceeded 100 °C/min at its maximum, indicative of a highly unstable compound. An ARC test performed on a pyridine solution of TBAP also indicated thermal instability and the exothermic decomposition started as low as 39 °C, although the rate of decomposition was slower than that observed for the neat solid TBAP (Figure 10).

In light of the DSC and ARC results, a decision to further evaluate the reaction by reaction calorimetry was made. The RC-1 test employed the addition of a cold pyridine solution of TBAP slowly to a 60 °C solution of the 4-bromo-2-nitrotoluene with the expectation that a higher solution temperature would eliminate the induction period. The resulting RC-1 heat flow curve (Figure 11) revealed that the reaction was an exothermic, feed-controlled addition (the green feed line and the orange conversion line are parallel and indicative of a feed-controlled scenario). A noticeable, yet manageable induction period was still observed at 60 °C during the initial stages of the reaction (demonstrated by the lack of deflection in the orange conversion line relative to the green feed line). Once the reaction began, an initial large exotherm was observed (evident by the sharp spike of the red line) that quickly subsided as the reaction progressed. After the large exotherm subsided, the reaction equilibrated and then proceeded smoothly with a controlled heat generation rate (red heat flow curve) as the TBAP/pyridine solution was fed into the reactor in a controlled manner. The reaction was completed in 2.5 h and an approximately 80% isolated yield of product was obtained.

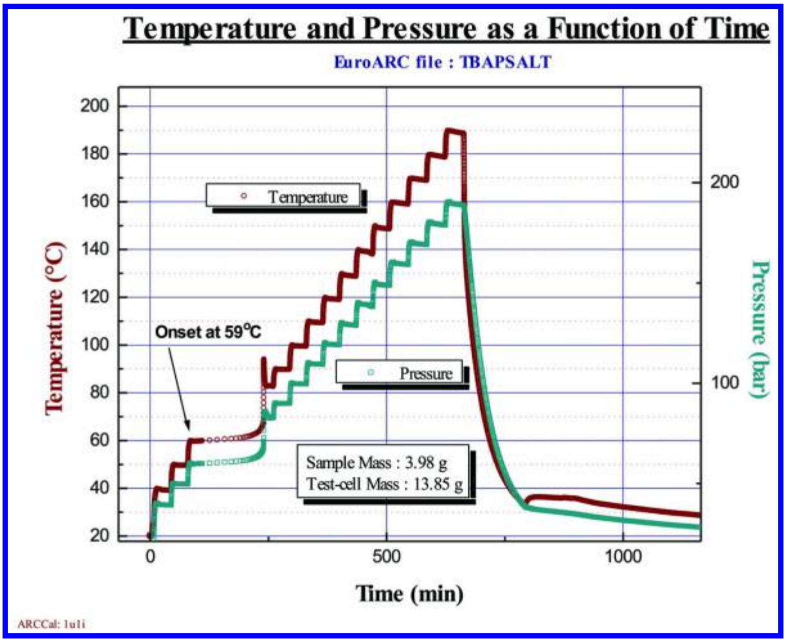


Figure 9. ARC test on TBAP. Reproduced with permission from reference (15). Copyright (2006) American Chemical Society (see color insert)

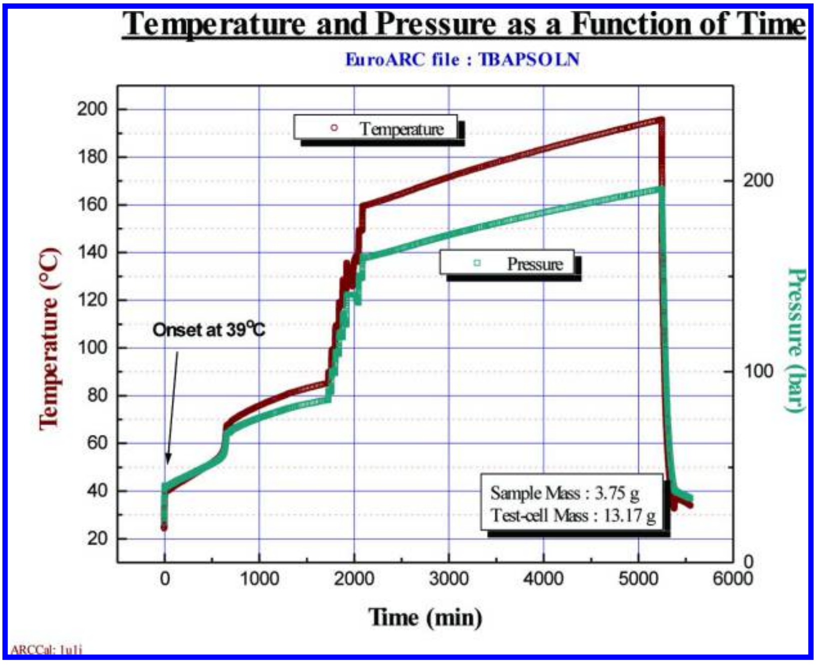
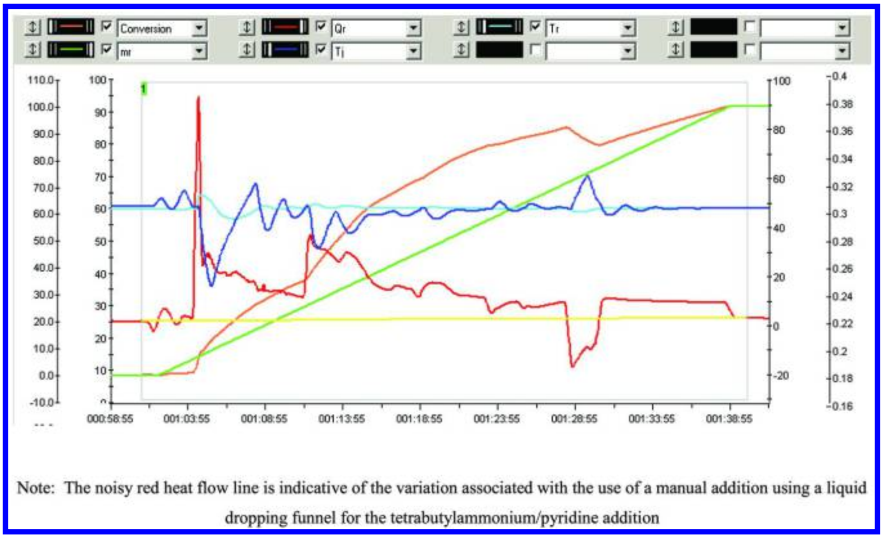


Figure 10. ARC test on a TBAP solution in pyridine. Reproduced with permission from reference (15). Copyright (2006) American Chemical Society (see color insert)



Note: The noisy red heat flow line is indicative of the variation associated with the use of a manual addition using a liquid dropping funnel for the tetrabutylammonium/pyridine addition

Figure 11. RC-1 test of oxidation reaction with TBAP in pyridine at 60°C. RC-1 Heat Flow Curve for Portion-wise controlled solution addition. Orange = Thermal conversion to product; Red = Heat flow (ΔH_{rxn}); Green = TBAP/pyridine feed; Dark Blue = Jacket temperature Tj; Light Blue = Reaction temperature Tr. Reproduced with permission from reference (15). Copyright (2006) American Chemical Society (see color insert)

Even with these improvements, the unpredictable induction period was still present and the reaction remained vigorously exothermic. This, coupled with the RC-1 heat flow results and the DSC and ARC results, led to the conclusion that these particular oxidation reaction conditions were not safe for large scale synthesis. The reaction scale was limited to 50 g scale and only carried out to supply material to meet the early project demands.

Most importantly, the reaction safety evaluation process that was carried out at this very early stage of synthesis development for this particular project allowed the chemistry team to recognize and appreciate the potential reaction safety hazards associated with scaling up these particular reaction conditions. This recognition allowed the team to make an informed decision and determine the “safe reaction space” to better define their level of acceptable risk and limit the reaction scale to 50 g. It was eventually decided that other oxidation methodologies would need to be investigated and developed to support the project had the project required larger drug substance supplies.

Conclusions

Strategies, tools, resources and examples of how best to approach identifying the potential chemical reaction hazards in the small scale research have been discussed. The need for the recognition of potential reaction safety issues coupled with the appropriate reaction safety testing at the early stages of research is valuable to establish a basis for safety for working in the chemical laboratory particularly at the early small scale stage of research and development. The reaction safety issues arising from chemicals, reactions and rates and/or the operational mechanics of the reaction can in most cases be subsequently rectified when identified early. The early identification of potentially serious hazards combined with elimination of these hazards and introduction of safer chemical alternatives are the basis for safe operation and safety of personnel. It usually also results in a significant cost savings as the chemistry progresses from initial research along the development pathway to final manufacturing. Modern instrumentation, chemical knowledge, dedicated personnel and most of all an attitude of 'safety comes first' is the key for preventing accidents and producing valuable process science.

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Chapter 5

Systems and Protocols for Evaluating Hazardous Reaction Issues During Early Stage Chemistry

Ryo Sugiyama* **and Toru Yamano**

Environment & Safety Department, Takeda Pharmaceutical
Company Limited, 17-85, Jusohonmachi 2-chome, Yodogawa-ku,
Osaka 532-8686, Japan
***E-mail: ryou.sugiyama@takeda.com**

We describe our approach and protocols for investigating new chemisty at Takeda during preliminary stages of new projects. Hazards from interactions between certain substances with reagents or solvents were assessed by simple methods which provided useful information quickly and accurately. Hence, examples of chemistry such as potassium *t*-butoxide with polar aprotic solvents, sodium borohydride with *N,N*-dimethylformamide or *N,N*-dimethylacetamide, rust with alkyl halides, rust and additives with cumene hydroperoxide, metals with hydrogen peroxide, and rust with hydrazine were investigated. The methods we describe are complementary to instrumental analyses, such as various types of reaction calorimetries and accelerating rate calorimetry, and provide preliminary information on the safety of chemical processes we wish to conduct in our laboratories and manufacturing plants.

Introduction

In March 1990, an explosion occurred at a manufacturing plant that produced 2,4-difluoroaniline by catalytic hydrogenation of the distilled 2,4-difluoronitrobenzene. 2,4-Difluoronitrobenzene is manufactured by halogen exchange of 2,4-dichloronitrobenzene with potassium fluoride in *N,N*-dimethylacetamide (DMAc) (*1*). The explosion was a result of a cascade of reactions initially triggered by the unintended introduction of water via recycled

DMAc. While such a reaction would not be intuitively obvious to most chemists, had sufficient investigations been conducted before scale up, it is likely this danger would have been appreciated and appropriate steps taken to avoid the occurance on scale. The lesson learned from this accident is that the process/plant designs for large-scale reactions must consider possibilities beyond the obvious chemistry that may occur.

Similar examples of unintended hazardous reactions are not uncommon for pharmaceutical manufacturers which handle thousands of compounds in small and large quantities, and use and produce a wide variety of hazardous materials. It can be difficult to understand all the variations of hazardous reactions that may occur between even a limited number of chemicals. As part of a total safety program, a full effort must be extended during the prelimnary stages of investigation to find hazards, particularly those that can lead to disasters. Generally, information on the hazards of intermediates and candidate compounds are limited because of their diversity and novelty. Therefore, there is a need to determine if each compound that will be used or produced has risks of explosion or for violent decomposition when exposed to catalysts, heat, impact, or friction, especially before any large scale work is considered.

Consequently, in pharmaceutical manufacturing, the comprehensive management of risks related to both compounds and processes using these compounds is required throughout all development stages. We will relate our experiences at Takeda handling hazardous chemicals and processes while still at small scale and for the purpose of building knowledge for ultimately commercial production.

Hazard Evaluation Systems; An Overview

Takeda Pharmaceutical Company Limited has established in-house procedures for hazard evaluation to comprehensively assess the risk of explosion for specific chemicals over the various stages that they can interact (shipping, storage, reaction, formulation, etc) (*2*). These hazards, which fall mainly into the categories of explosive decomposition hazards, chemical reaction hazards, and dust explosion hazards, are shown in Table I along with our standard and advanced testing protocols.

We make use of both in-house and external hazard evaluation organizations to obtain potential risk information to design our nascent processes. Fire and explosion hazards are evaluated first using a broad screening test followed by standard tests and, ultimately, advanced tests to assess the risks of raw materials, intermediates, solvents, catalysts, and candidate compounds. The sophistication of the tests depends on the development stage. As a screening test, sealed cell differential scanning calorimetry (SC-DSC) generates primary data on the potential energy and risks associated with heating of a substance. The need for further tests to assess the risk of explosive decomposition of a substance is determined based on the results of the initial screening tests. Different standard tests are used to determine explosive decomposition hazards, chemical reaction hazards, and dust explosion hazards. Advanced tests may then be required if it is clear additional data is required.

In all cases, we conduct safety meetings before scaling up further or moving to advanced pharmaceutical manufacturing or formulating. The discussions at these meetings include:

- Confirmation of the protocols for hazard evaluation
- The implementation of safety measures identified based on the available risk information.
- Evaluation of the safety measures to prevent fire and explosion
- Evaluation of the occupational exposure management systems designed to protect the health of employees.
- Safety audits conducted both in house and by external resources.

Figure 1 shows schematically our work flow for considering safe practices throughout the development cycle.

Chemical Reaction Processes Risks

Many synthetic organic reactions used for the synthesis of pharmaceuticals, such as nitration, the Vilsmeier reaction, and Grignard reagent preparation, are highly exothermic. To establish reaction processes suitable for large-scale synthesis, it is necessary to evaluate the risk of runaway reactions caused by a such exothermic events.

Highly active reagents are most often used during the early stages of development because it is advantageous to shorten the development period by the use of fast acting reagents and it is likely these reagents had been used in the initial synthesis of the compound. Examples of highly reactive reagents include organometallic compounds, organic peroxides, and self-reactive substances. The use of such highly reactive reagents provide fast reactions and high conversions but may lead to the formation of unstable byproducts whose decomposition can generate large quantities of energy. Unexpected reactions in general can occur when the reaction temperature overshoots the specified conditions. Thus, to establish a safe reaction process, it is necessary to thoroughly consider all of the risks that may arise as a consequence of deviations from the desired reaction conditions.

These issues become critical when carrying out large scale reactions in which additional unexpected hazardous reactions are possible from impurity catalysis (e.g. rust), poor mixing (hot spots) and unstable volatiles collecting in low spots in overhead equipment. Because it can be difficult to perfectly clean and/or operate a reactor, effort should be made to ensure that expected impurities are carefully considered at the time of scale-up. Therefore, risk assessments must be conducted from various perspectives and parameters well outside the targeted reaction conditions in order to appropriately evaluate the risks associated with a chemical reaction.

Table I. Hazard evaluation items

Hazards	*Standard tests*	*Advanced tests*
Explosive decomposition hazards (heat, impact, and friction)	Heat - Sealed cell differential scanning calorimetry (a screening test) - Pressure vessel test Impact and friction - Drop hammer test - Friction test	Heat Accumulation - Heat accumulation storage test Detonation - BAM 50/60 steel tube test[a,b] - MKIII ballistic mortar test - UN deflagration test Ignitability and combustibility - BAM ignitability test*a* - IMO combustibility test[c]
Runaway reaction hazards	Heat of reaction measurement - Reaction calorimetry (RC-1) - Accelerating rate calorimetry (ARC) - Differential reaction microcalorimetry	Mixing hazards/unexpected reaction - Dewar flask test - Heating test by test tubes
Dust explosion hazards	Dust property - Volume resistivity measurement - Distribution of particle size by sieving Safety evaluation for dust explosion - Lower explosive limit - Minimum ignition energy - Explosion limiting oxygen concentration	Safety evaluation for dust explosion - Characteristics of explosion pressure

[a] BAM: Federal Institute for Materials Research and Testing in German. [b] 50/60 steel test: Test sample filled in a sealed steel tube are detonated with a detonator to judge the property of detonation based on the destruction condition of the steel tube. [c] IMO: International Martime Organization.

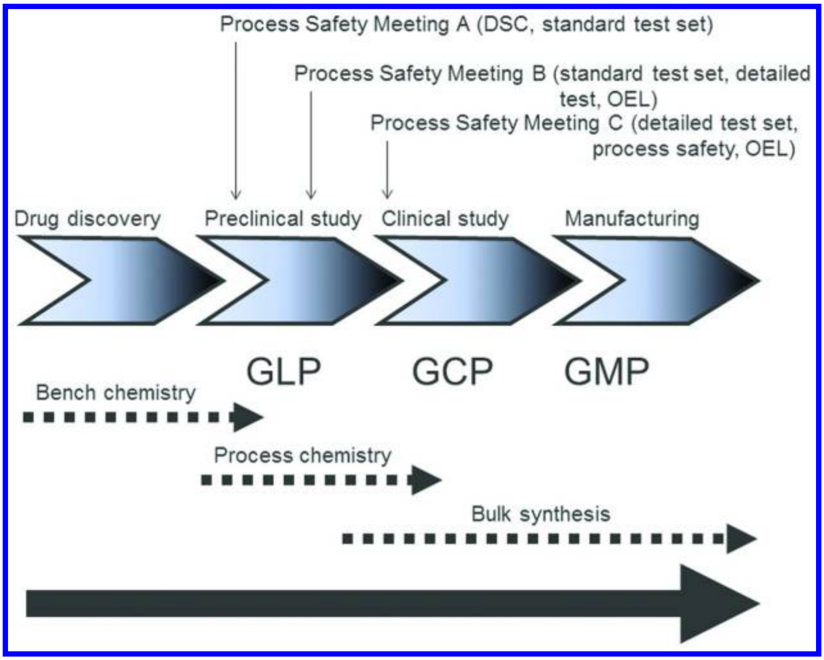


Figure 1. Process safety meeting schematic

Examples of risks to be considered :

- Runaway exothermic reactions caused by a cooling failure
- Decomposition as a result of a runaway reaction or overheating
- Generation of dangerous side reactions and/or dangerous byproducts when reaction conditions deviate from the specified conditions
- Generation of hazardous gases that are explosive, irritants, corrosive or may spontaneously combust as a result of unexpected decomposition or side reactions
- Dangerous increases in the internal pressure as a result of gas generation
- Unexpected reactions caused by impurities, such as rust, acids, or bases
- Impurity catalysis leading to energetic decomposition at lower temperatures than expected

When assessing the overall risks, it is important to understand that explosions may be initiated by heat, impact, or friction. When handling self-reactive substances in reaction mixtures, the possibility of a decrease in the stability due to the catalytic effect of other entities in the reaction mixture should be carefully examined. Material Safety Data Sheets (MSDSs) provide the known hazards for most raw materials. Assumed hazards may be predicted for self-reactive substances based on the presence of functional groups known to release high levels of energy. Examples of these functional groups include nitro groups, diazo linkages, organic peroxides and many others. A good source of information on suspect moieties are found in Bretherick's Handbook of Reactive Chemical Hazards (*3*).

Various types of calorimetries and systematic methods for the assessment of the risk for a runaway reaction or the decomposition of self-reactive substances have been developed. For example, the impact of an exothermic runaway reaction is assessed by measuring the temperature increase that would occur in an insulated reactor in the event of a cooling failure. Key issues would also be the boiling point of the solvent and the heat of reaction. The risk/impact of an explosion due to the decomposition of self-reactive substances following a runaway reaction after an induction time is often assessed using accelerating rate calorimetry (ARC) (*4–7*).

In the following sections, we describe typical examples of safey investigations that make use of simple tools and our approaches to understanding chemical reaction hazards. These cases all involve the unexpected participation of materials or unexpected reactions, resulting in the potential for decomposition or undesired exothermic reactions.

Mixing Hazards of Reagents with Organic Solvents

Butoxide

Potassium *tert*-butoxide (*t*-BuOK) is widely used as a weakly nucleophilic but strong base in synthetic organic reactions (*8*). While most chemists don't consider this a hazardous reagent, it can cause fires. Generally, this strong base is used in solvents such as tetrahydrofuran (THF) or those exhibiting a certain level of polarity to enable solubility. Allowable solvents don't possess acidic hydrogens but there can be other restrictions as well. For example, certain polar solvents, such as those containing halides, ketones, and esters may ignite upon contact with solid *t*-BuOK (*9*).

Ignition has been also reported upon *t*-BuOK addition to dimethylsulfoxide (DMSO) (*10*). However, the prioritization of yield and solubility over the danger of ignition might still justify the use of DMSO in most cases, as for the Wolff–Kishner reduction (*11*) if the hazards are well understood and operations are maintained within safe parameters.

Takeuchi *et al.* used Dewar flask tests to assess the hazards of *t*-BuOK when mixed with organic solvents (*12*). The use of *t*-BuOK had not been previously recommended for commodity chemical production because of the ignition danger occurring upon mixing with some organic solvents. The pioneering work of these researchers established that a nitrogen atmosphere was sufficient to sufficiently reduce the ignition risk and justified the use of the specific solvent in some cases (*12*). This work suggested to us to extend the technique to our investigations.

A Dewar flask test (Figure 2) is a readily available and inexpensive fundamental test that is suitable for screening large numbers of reactions quickly. About 20 mL of sample is sufficient to screen a sample's risk of ignition in a 100 mL Dewar flask. The test can be conducted safely using a drip funnel equipped with a solenoid valve to mix reagents and organic solvents. The insulating container maintains an adiabatic system and facilitates the measurement of exothermic events. Continuous internal sample temperature measurements are recorded by a thermocouple and also follow state change (ignition, browning, or gas generation).

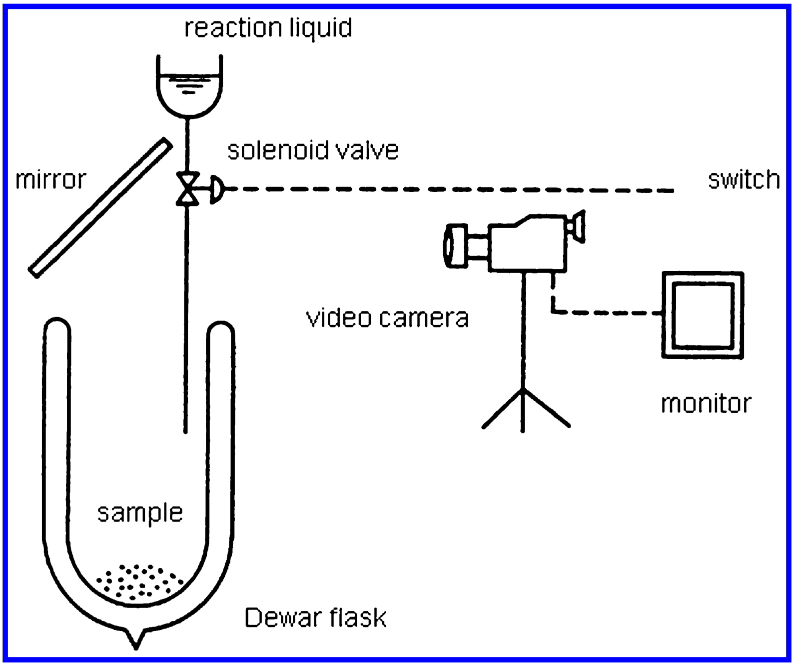


Figure 2. Dewar vessel test apparatus. Reproduced with permission from reference (12). Copyright (1996) Japan Society for Safety Engineering.

We examined the reproducibility and utility of the Dewar flask test results for a Takeda project involving base and solvents (Table II). Potassium or sodium butoxide powder (1.5 g) was mixed with solvents added dropwise (0.5 mL) or contacted with organic vapors generated from solvent reservoirs (15 mL). Our Dewar flask tests exhibited no ignition events, unlike some of the previous reports. However, some solvents did lead to browning and fumes upon contact with butoxides. The presence of small amount of impurities, such as metallic potassium, in low-purity *t*-BuOK may explain the ignition results for others (*10*).

These varying results compared to the published sources may indicate that ignition phenomena depend on other factors such as reagent impurities, particle size, mixing speed, contact area with air, and heating rate. Therefore, the decision to claim a Dewar flask test reaction safe based only on the absence of ignition should be carefully considered and not taken as the only indication that it is a safe process. Clearly it is best to consider each larger scale process as an unique example and to test the actual material to be used along with the actual solvents and using the same operational sequence, materials of construction, etc, as will be used on scale in order to produce a proper test.

Table II. Mixing hazards of alkali *t*-butoxides with organic solvents[a,b]. Reproduced with permission from reference (*12*). Copyright (1996) Japan Society for Safety Engineering.

Solvent	*Literature data*				*Experimental value*	
	Manwaring et al[c]		*MCA Case History No. 1718*[d]	*Takeuchi et al*[e]	*Authors*	
	t-BuOK	*t-BuOK*	*t-BuOK*	*t-BuOK*	*t-BuOK*	*t-BuONa*
	Droplet	*Vapor*	*Droplet*	*Droplet*	*Droplet*	*Droplet*
Methanol	I (2 min)			F	ND	ND
Ethanol		I (7 min)				
Propanol	I (1 min)					
2-Propanol	I (1 min)			ND		
Methyl acetate					B	B
Ethyl acetate		I (2 min)			B	B
Butyl acetate		I (2 min)				
Methyl propionate					B	B
Propyl formate		I (4 min)				
Dimethyl carbonate	I (1 min)					
Diethyl sulfate	I (1 min)					
Acetone	I (2 min)	I (4 min)		I (70 s), B[f]	ND	B
Ethyl methyl ketone	I (30 sec)	I (1 min)			ND	B

Solvent	*Literature data*				*Experimental value*	
	Manwaring et al[c]		*MCA Case History No. 1718*[d]	*Takeuchi et al*[e]	*Authors*	
	t-BuOK	*t-BuOK*	*t-BuOK*	*t-BuOK*	*t-BuOK*	*t-BuONa*
	Droplet	*Vapor*	*Droplet*	*Droplet*	*Droplet*	*Droplet*
3-Pentanone					F (3 min)	F (30 s)
Dichloromethane	I (2 min)				F (2 min)	ND
Chloroform	I (0 min)	I (2 min)		I (0 min), F[f]	F (0 min)	F (0 min)
Tetrachloromethane	I (1 min)			I(15 s), F[f]	B	ND
1-Chloro-2,3-epoxypropane	I (1 min)					
Dimethyl sulfoxide			I (0 min)		ND	ND
Toluene				ND		

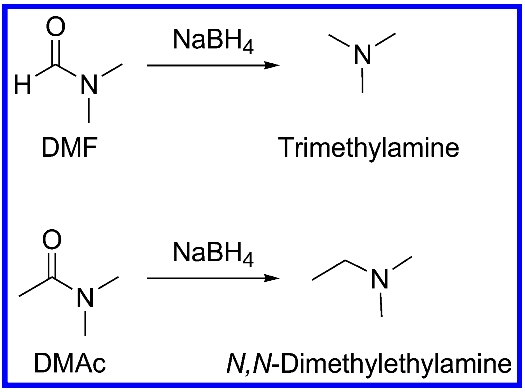
[a] I: Ignition; F: Fuming; B: Browning; ND: Not detectable. [b] The numerical data in brackets represents the amount of time required to cause ignition.

[c] Data from reference (*9*). [d] Data from reference (*10*). [e] Data from reference (*12*). [f] Data under nitrogen purging.

Dewar flask tests are important in the evaluation of mixing hazards but have their limitations. These tests are primarily useful for a first pass assessment of the mixing risk between solvents and reagents. As such, they are a part of a plan for ascertaining the safety of a process and require additional investigations of the other aspects of a reaction and its workup.

Sodium Borohydride

Sodium borohydride ($NaBH_4$) will reduce carbonyl compounds, such as ketones and aldehydes, into their corresponding alcohols. Alcohols, such as methanol and ethanol, are the preferred solvents. Other organic solvents and complexing agents can also used to control the reduction power and selectivity of $NaBH_4$. It is possible to use versatile aprotic solvents bearing a carbonyl group, such as *N,N*-dimethylformamide (DMF) and *N,N*-dimethylacetamide (DMAc). However, these are reduced by $NaBH_4$ at elevated temperatures to produce pyrophoric trimethylamine and *N,N*-dimethylethylamine (Scheme 1), respectively, and are not commonly used (*13*, *14*).



Scheme 1. Reduction of DMF and DMAc by $NaBH_4$

Shimizu *et al.* demonstrated that $NaBH_4$ was more thermally stable in DMAc as compared to DMF through sealed-cell differential scanning calorimetry (SC-DSC) and accelerating rate calorimetry (ARC) measurements (*15*). We decided to extend these investigations to determine the safety margins for using these solvents for a reduction we intended to scale up.

We investigated the mixing hazard of DMF and DMAc with $NaBH_4$ by a simplified flask test which includes the observation of appearance, gas generation, and spontaneous ignition (Table III). Figure 3 shows photos of the results from some of these tests. When DMF was utilized as a solvent, the induction times to spontaneous ignition amounted to 44, 15, and 6 min at the holding temperatures of 102, 122, and 132 °C, respectively. When DMAc was used as a solvent, *N,N*-dimethylethylamine was generated but no ignition occurred. This suggests that DMF carries a higher risk.

Table III. Chemical reaction hazards of sodium borohydride and aprotic solvents[a]

Run No.	*Solvent*	*Sample mass*		*Initial temperature (°C)*	*Induction time*	*Maximum temperature (°C)*	*Results of observation*
		Solvent (mL)	*$NaBH_4$ (g)*				
1	DMF	17	3	102	43 min 40 s	272	Ignition
2				122	14 min 30 s	233	Ignition
3				132	5 min 40 s	250	Ignition
4	DMAc	17	3	132	None[b]		
5				162	7 min	170	Reflux and bumping

[a] Original data. [b] No temperature change occurred for 60 min.

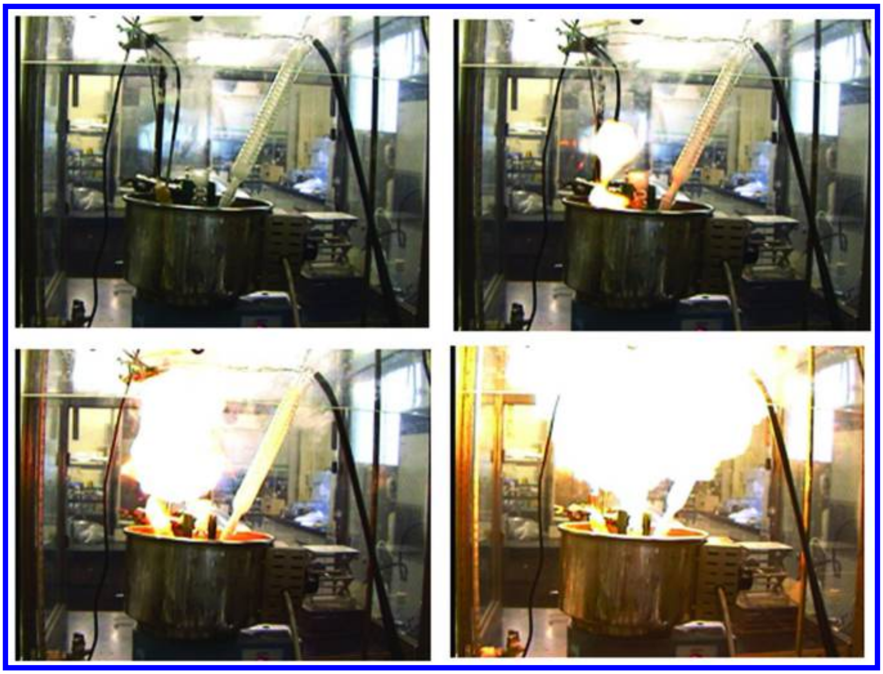


Figure 3. Results of mixing DMF and sodium borohydride. These photographs are taken by the authors.

There are many factors that will determine whether ignition will occur when adding a solvent to $NaBH_4$. These factors include rate of gas generation, temperature, contact with air, and the heat radiation speed for pyrophoric gas generation. Thus, even if no ignition occurs during the flask-scale experiments, spontaneous ignition is still possible on large scale if the reaction conditions are not exactly the same. Changes related to the above mentioned factors should be carefully reassessed before scale-up. This is a crucial assessment that will identify the conditions needed to prevent spontaneous ignition between solvents and reducing agents. It is important to identify the lower temperature limit for safe opearation where pyrophoric gases are not generated. If pyrophoric gas generation is inevitable, then measures that prevent spontaneous ignition such as the use of cooling gas in addition to an inert-gas atmosphere are required. ARC and heat accumulation storage tests will determine the lower limit temperatures where undesired reactions begin to occur.

Our flask-scale experiments were not conducted adiabatically. Therefore, the upper limit temperatures for safe operation may be lower for a large scale synthesis than for flask-scale experiments because there will be more heat accumulation on scale. Although the simplified flask-scale experiments are relatively crude, they are reliable and offer fundamental information on pyrophoric gas generation, ignition phenomena, and the relationship between induction time and reaction temperature. Therefore, these flask-scale experiments are useful in understanding the possible risks of spontaneous ignition at early stages of process development.

Organic Halides

Organic halides can take part in numerous reactions, such as elimination, substitution, metallation, etc. Further reactivity may result if the halide is in an activated position such as benzylic or allylic. Impurities such as acids, bases, and rust can sometimes serve as catalysts for material decomposition and lead to undesired reactions for organic halides. For instance, a mixture of a polyhalogenated hydrocarbon (for example tetrachloromethane or 1,2,3,4,5,6-hexachlorocyclohexane) and tertiary amides (such as DMF and DMAc) may react violently in the presence of iron (*16*, *17*). However, this kind of behavior is not limited to polyhalogenated hydrocarbons. The monohalogenated hydrocarbon, benzyl chloride, underwent an unexpected decomposition when stored in a tank containing traces of rust. This decomposition resulted in a rapid generation of hydrogen chloride and consequently breaching of the tank (*18*).

ARC and reaction calorimetry are generally used to assess the risks of unexpected reactions of organic halides once screening tests have been completed. Sealed-cell DSC can determine the thermal stability of chemical substances, but is unsuitable for exploring the effect of impurities because it requires sample amounts that are too small (up to a few mg) to add reproducible quantities of solid impurities. this led to the development of heating tests in test tubes for screening the risks of impurity-induced reactions for organic halides.

Kotoyori *et al.* monitored the heat induced state change of mixtures in test tubes in an aluminum block using a DTU-1C device (*19*). We designed a similar test apparatus that is equipped with an aluminum block heated with a custom-fabricated heating mantle. The heating mantle permits a wider temperature range and tunable heating rates (Figure 4). Mixed test samples and reference materials are heated in parallel and the temperature is measured using a Teflon coating thermocouple.

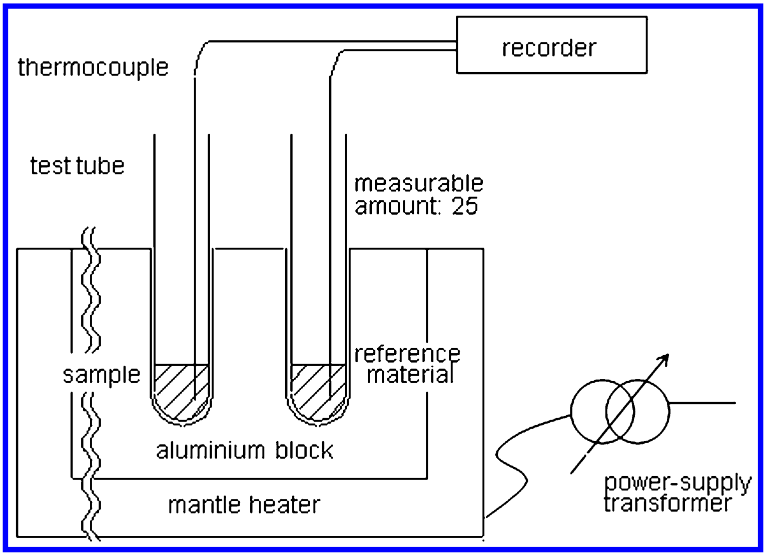


Figure 4. Heating test device using test tubes

Open test tubes facilitated the observation of state changes (browning, decomposition, burning, gas generation, and explosion) in mixed samples although air would always be a factor as well. Deviations in temperature from the heating rate provided insight into the exothermal behavior of these samples.

As a representative example, we tested a solution of benzyl chloride in DMAc mixed with iron powder or rust. Our team decided to use benzyl chloride/Fe combinations as a case study because of the forementioned accident. DMAc (2.0 mL) was poured into a test tube followed by benzyl chloride (1.0 g) and iron (metallic Fe, FeO or Fe_2O_3) (1.0 g) .

The exothermic behavior was analyzed based on the difference in temperature rise between the test sample and a reference tube containing just silica-gel. State changes of the mixed samples in a test tube and gas generation was observed and recorded (Table IV).

Table IV. Results of mixing an organic halide with DMAc, effect of iron containing impurities[a,b,c]

Run No.	*Organic halides*	*Sample mass of impurities*			*Results*
		Iron powder	*Black rust*	*Red rust*	
1	None (DMAc alone)	none	none	none	ND
2	Benzyl chloride	1.0 g	none	none	ND
3	Tetrachloromethane	1.0 g	none	none	E
4	Benzyl chloride	none	1.0 g	none	ND
5	Tetrachloromethane	none	1.0 g	none	F
6	Benzyl chloride	none	none	1.0 g	ND
7	Tetrachloromethane	none	none	1.0 g	ND

[a] Original data. [b] E: Noticeably exothermic; F: Fuming; ND: Not detectable. [c] Test conditions: Organic halide (1.0 g) and impurity (1.0 g) were mixed in *DMAc* (2.0 mL).

We also included the tetrachloromethane–DMAc-iron test mentioned above to validate our method (run No. 3) and it exothermed as expected. Tetrachloromethane reacted with DMAc to generate fumes in the presence of black rust (run No. 5). In contrast, the same mixture but with red rust (Fe_2O_3) (run No. 7) was unreactive. The reactivity of tetrachloromethane and DMAc differed according to the state of the coexisting iron. No noticeable exothermic reaction was observed when benzyl chloride was mixed with DMAc in the presence of metallic iron or metal ion (runs No. 2, 4, 6). This approach serves as a screening method for assessing the risks of unexpected reactions caused by trace impurities.

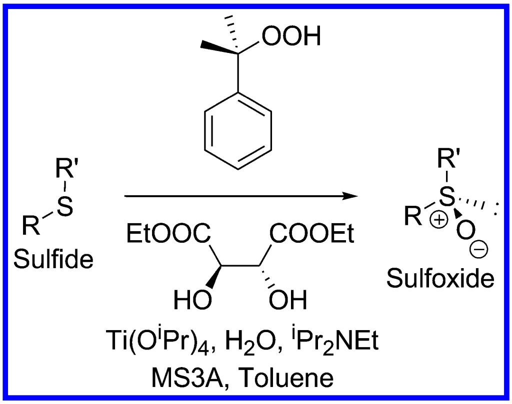
Handling Self-Reactive Compounds

Cumene Hydroperoxide

Cumene hydroperoxide (CHP) is an organic peroxide that serves as a polymerization initiator and an oxidizing agent in organic synthesis. Because of its self-reactivity, this peroxide may explode upon heating. It is similar to other organic peroxides, such as benzoyl peroxide, methyl ethyl ketone peroxide, *tert*-butyl hydroperoxide, and dicumyl peroxide, which have also exploded during storage, reaction, distillation, and drying processes (*20*). While CHP is a useful and valuable chemical, clearly additional safety understanding is required to use it safely.

Many researchers have investigated the risks of heating CHP and its decomposition kinetics (*20–22*). Duh *et al.* reported the effects of impurities, such as acids, alkalis, and ferrous ions, on heat decomposition of CHP (*23*). In addition, Hou *et al.* studied the decomposition of CHP in the presence of alkali catalysts (*24*). However, the effects of many other substances and impurities on organic peroxides remains unclear.

We were interested in the asymmetric oxidation of sulfides with CHP (Sharpless–Kagan oxidation, Scheme 2), thus we wished to understand the effects of coexisting substances and minute amounts of impurities, such as rust, on the thermal stability of the peroxide as a precursor to scale up.



Scheme 2. Asymmetric oxidation of sulfide with CHP (Sharpless–Kagan oxidation)

One concern is the thermolysis risk of CHP due to a runaway reaction leading to overheating. Another issue would be lowering of the temperature at which the exothermic decomposition of CHP begins, catalyzed by coexisting substances or small amounts of impurities in the reaction mixture.

CHP is often handled as a cumene solution. We used the cumene solution from NOF Corporation Percymyl H-80, which contains 81% CHP. When conducting asymmetric oxidations, the sulfide raw material was dissolved in toluene and 3A molecular sieves were added to the solution. Titanium(IV) tetraisopropoxide (TTIP), diethyl L-(+)-tartrate, and water were subsequently added to form the asymmetric catalyst complex. *N*-Ethyldiisopropylamine was stirred into the mixture before the addition of CHP cumene solution.

The effects of toluene on the thermal stability of CHP were investigated. A 2.0 mL aliquot of CHP cumene solution was placed in a test tube, and then toluene was added as needed. Three different tests were conducted: neat, with 2.0 mL and with 5.0 mL toluene.

In all cases, the onset temperature for the exothermic decomposition of CHP began at 150 °C, as compared to 168 °C when SC-DSC was run (*25*). In another test, the CHP solution in toluene was heated at 120–130 °C until all the solvent had evaporated. The temperature remained constant until the evaporation was complete, at which point the temperature of the test sample continued to rise until the decomposition of CHP started at 150 °C. This demonstrated that the onset temperature for the exothermic decomposition of CHP is not affected by the presence of toluene as solvent.

The effects of coexisting substances on the thermal stability of CHP were investigated by heating an aliquot of CHP cumene solution (2.0 mL) and coexisting substances (1.0 g) in test tubes. The sulfide as raw material, 3A molecular sieves, diethyl L-(+)-tartrate, and *N*-ethyldiisopropylamine were chosen as coexisting substances (Table V).

Table V. Onset temperatures for the exothermic decomposition of CHP in the presence of coexisting substances[a,b]

Run No.	*Coexisting substances*	*Observed onset temperature (°C)*
1	Sulfide (raw material)	88
2	Diethyl L-(+)-tartrate	150
3	*N*-Ethyldiisopropylamine	60
4	MS3A (passed through 200 mesh (75 μm))	120
5	None (CHP cumene solution alone)	150

[a] Original data. [b] Test conditions: A coexisting substance (1.0 g) was added to 2.0 mL of CHP cumene solution without toluene.

When CHP was heated in the presence of sulfide, *N*-ethyldiisopropylamine, and 3A molecular sieves, the onset temperature for its exothermic decomposition was below the benchmark of 150 °C. In addition, the results indicated that sulfide and *N*-ethyldiisopropylamine had significantly decreased the thermal stability of CHP. 3A Molecular sieves had a smaller impact on the thermal stability of CHP. In contrast, diethyl L-(+)-tartrate showed little effect.

The effects of impurities, such as rust, on the thermal stability of CHP were investigated by heating an aliquot of CHP cumene solution (2.0 mL) in a test tube in the presence of powdered impurities (1.0 g). Copper powder, iron powder, black rust, and red rust served as impurities (Table VI). Thre are reports that CHP decomposes in the presence of copper (*26*), thus it was included.

Table VI. Onset temperatures for the exothermic decomposition of CHP in the presence of metal impurities[a,b]

Run No.	*Coexisting substances*	*Observed onset temperature (°C)*
1	Copper powder	85
2	Iron powder	95
3	Black rust	75
4	Red rust	95
5	None (CHP cumene solution alone)	150

[a] Original data. [b] Test conditions: The coexisting substance (1.0 g) was added to 2.0 mL of CHP cumene solution without toluene.

When CHP cumene solution was heated in the presence of individual metal powders, the onset temperature for the exothermic decomposition of CHP were all well below 150 °C, indicating that all metallic impurities will need to be carefully monitored in our reactions.

For compounds that can self-decompose, it is necessary to consider the possibility of reduced thermal stability resulting from other substances to be used in the reaction as well as small amounts of impurities, such as rust. Examination using test tubes are simple and easily enable varying different factors.

Hydrogen Peroxide

Hydrogen peroxide (H_2O_2) is a powerful oxidizer, usually distributed as a realtively safe 30% aqueous solution although high-concentration H_2O_2 solutions are also available. Solutions of H_2O_2 are unstable and gradually decompose in the presence of impurities, although stabilizers will extend the useful life of the solution. It commonly serves as a bleaching agent for paper, pulp, and fabric; a surface treatment agent for metallic species; an oxidizing agent and polymerization catalyst in organic synthesis; a sterilizing agent for packaging containers; a medical disinfectant; an alternative to formalin fumigation; and finds numerous environmental applications in wastewater treatment. Because it decomposes into water and oxygen, it is considered to have a small environmental load and has been considered a 'green' oxidant.

On the other hand, the use of concentrated H_2O_2 has potential risks, including spontaneous ignition of combustible substances, detonation, and over-pressurization of vessels or containers. These risks have been widely investigated and reviewed (*27–30*).

Considering its known hazards, we thought it was prudent to explore fire and explosion phenomena, which are caused by rapid temperature rise resulting from mixing H_2O_2 with combustible substances, and bursting phenomena, which are caused by rapid oxygen generation resulting from H_2O_2 decomposition. In addition to the effects of trace amounts of impurities, such as dust, and heavy metal ions, the effects of pH and surface activation on the stability of H_2O_2 solutions are summarized below.

Spontaneous Ignition Risks

H_2O_2 solutions will not burn on its own, however they can start a fire upon contact with a combustible substance (*27–29*). At high concentrations, the temperature increase associated with H_2O_2 decomposition is extremely high, allowing a combustible substance in contact with the solution to easily catch fire. Wood, straw, rags, and clothing soaked with a high-concentration H_2O_2 solution may ignite spontaneously, particularly if water evaporates from the wet organic material, further concentrating the entrained H_2O_2. Thus, even low concentration solutions should not be mixed with organic materials, as may occur in the event of cleaning up a spill.

The decomposition of H_2O_2 generates 98.2×10^3 J /mol of heat (*27*). Below 65% H_2O_2, even in case of self-decomposition, the energy produced is not sufficient to evaporate the coexisting water, and the temperature of H_2O_2 solution will not surpass its boiling point. However, concentrations above 65% produce sufficient energy upon decomposition to evaporate the water which concentrates the H_2O_2, raising further the danger potential.

Some physical properties of H_2O_2 solutions are shown in Table VII and maximum temperatures reached by the decomposition of H_2O_2 solution under adiabatic conditions are shown in Table VIII. When a 70% H_2O_2 solution decomposes, the mixture may reach a top temperature of 233 °C, however the potential maximum temperature may be much higher if the heat leads to the further concentration of the H_2O_2 titer.

Explosion Risks

Mixtures of highly concentrated H_2O_2 solutions and organic compounds should be considered for their risk of detonation (*27*, *29*, *30*). Mixtures of high concentration H_2O_2 solutions may detonate even with a small mechanical impact, such as dropping the container. In particular, metal particulates in H_2O_2 solution increase the potential risk of detonation.

Table VII. Physical properties of H_2O_2 solutions. Reproduced with permission from reference (*29*). Copyright (1970) Japan Society for Safety Engineering. Reproduced with permission from reference (*30*). Copyright (1980) The Chemical Society of Japan.

H_2O_2 (%)	*Amount of active oxygen (%)*	*Boiling point (°C)*	*Melting point (°C)*
30	14.1[a]	106[a]	−26[a]
35	16.5[a,b]	108[a], 107[b]	−33[a,b]
50	23.5[a,b]	114[a], 111[b]	−50[a,b]
60	28.2[a]	120[a]	−55[a]
70	32.9[b]	125[b]	−39[b]
90	42.3[b]	141[b]	−11[b]

[a] Data from reference (*30*). [b] Data from reference (*12*).

Table VIII. Maximum temperature reached due to H_2O_2 decomposition under adiabatic conditions. Reproduced with permission from reference (*29*). Copyright (1970) Japan Society for Safety Engineering.

H_2O_2 (%)	*Maximum temperature (°C)*
70	233
75	360
80	487
85	613
90	740
100	996

Detonation composition ranges for acetone, ethanol, and glycerin mixtures with H_2O_2 are shown in Figure 5. The large area for detonation gives an idea of the hazards of mixtures of H_2O_2 and organic solvents. The detonatability of mixtures comprising H_2O_2 and acetic acid, aniline, carbitol, 1,4-dioxane, ethyl acetate, ethyl cellosolve, ethyleneglycol, 2-propanol, methanol, methyl methacrylate, and quinolone, were investigated. When these solvents were added to 90% H_2O_2 solution until the solvent volume % reached 30%, the resulting solutions exhibited detonatability as dangerous as military explosives.

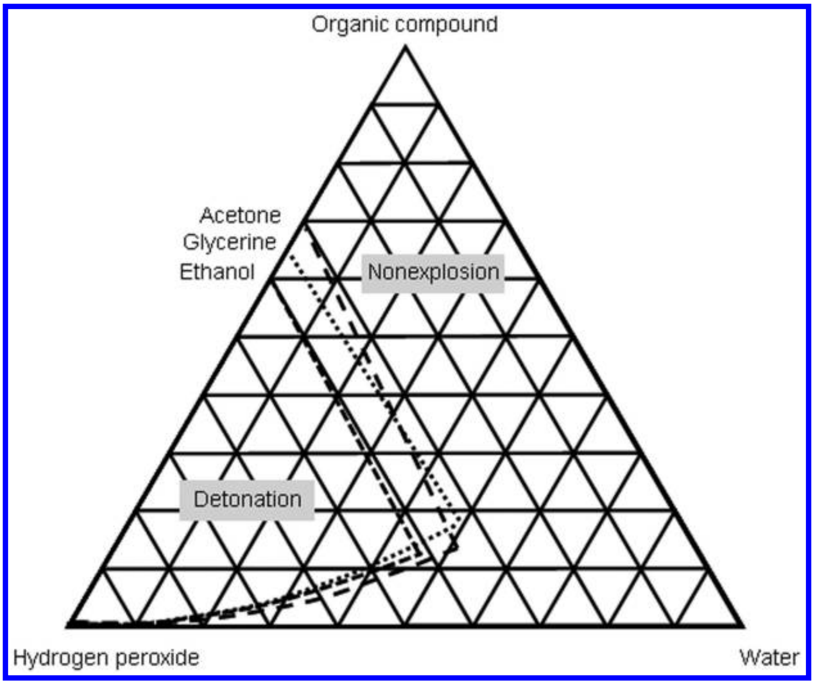


Figure 5. Detonation composition range of H_2O_2–water–organic compound mixtures. Reproduced with permission from reference (30). Copyright (1980) The Chemical Society of Japan.

The lower explosive limit of H_2O_2 vapor is 40%. A 40:60 H_2O_2 vapor/air gas mixture is equivalent to the equilibrium vapor concentration of a 74% H_2O_2 solution at boiling point. Therefore, at atmospheric pressure, if a H_2O_2 solution exceeding 74% is brought to a boil at 128 °C, the vapor concentration moves into the explosive range.

The explosion range of H_2O_2 vapor is shown in the shaded portion of Figure 6. The lower explosive limit of H_2O_2 increases with decreasing pressure. This limit equals 40% at atmospheric pressure but increases to 49% and 70% at 200 and at 40 mmHg, respectively. When the H_2O_2 vapor is in the explosion range, the existence of ignition sources, such as sparks, certain catalysts, and foreign contaminants, creates a strong possibility for an explosive decomposition.

Under ordinary storage and handling conditions, dangerous levels of H_2O_2 vapor within the explosion range should not form. However, heating a high-concentration H_2O_2 solution, whether on purpose or accidentally, or concentrating H_2O_2 in an experiment could generate H_2O_2 gas at dangerous concentrations. A H_2O_2 solution under vacuum is particularly prone to become concentrated excessively.

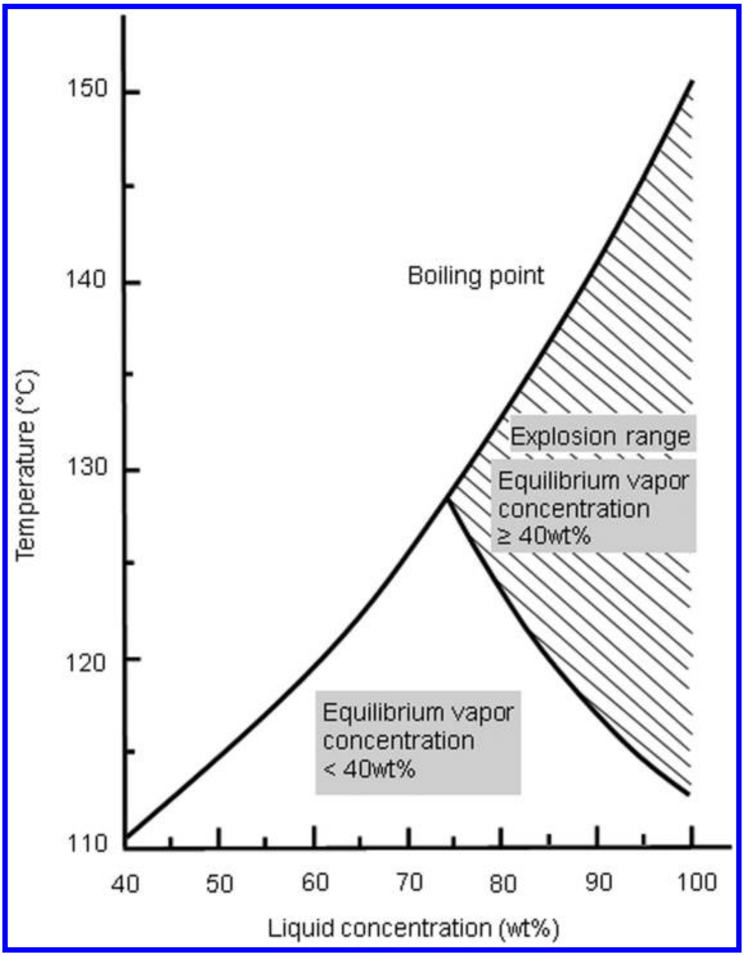


Figure 6. Risk range of high-concentration H_2O_2. Reproduced with permission from reference (30). Copyright (1980) The Chemical Society of Japan.

Bursting Risk Related to an Increase in Internal Pressure

When a H_2O_2 solution decomposes, oxygen and water are formed. When the H_2O_2 solution is enclosed in a sealed container, the container will resultingly pressurize and possibly burst. Therefore, avoiding contamination of H_2O_2 solutions is particularly important during storage to prevent catalysis leading to decomposition. This is accomplished by judicious selection of the material of composition for storage vessels and maintaining high purity in its preparation and storage. Ideally, the internal pressure of vessels should be monitored as well to detect pressure build-up before it becomes hazardous.

Effect of Heavy Metal Ions

H_2O_2 solutions may decompose explosively when mixed with certain trace impurities. The effects of Cu^{2+}, Fe^{3+}, and Fe^{2+} ions on initiating this decomposition have been studied in detail (*31–33*). Heavy metal ions in particular are known to catalyze the decomposition of H_2O_2.

Usually the principle danger occurs if a solution is stored in a sealed container and then decomposes to form oxygen gas. For example, in 1999, a tanker truck transporting a H_2O_2 solution exploded in transit. The truck usually transported waste solutions containing copper chloride. It is believed the residual copper caused H_2O_2 to decompose, leading to the explosion (*33*).

The effects of heavy metal ions added to 90% H_2O_2 and heated are shown in Table IX. Many types of heavy metal ions accelerate the decomposition of H_2O_2 solutions. Copper, iron, chromium, and manganese catalyze this decomposition even at low concentrations. On the other hand, magnesium, aluminum, zinc, and platinum display little catalytic activity and may be considered safer metals to use in chemistry associated with H_2O_2. H_2O_2 solutions are quite stable in the absence of impurities (*29*).

Table IX. Residual concentrations of active oxygen from metal-containing H_2O_2 solutions[a]. Reproduced with permission from reference (*29*). Copyright (1970) Japan Society for Safety Engineering.

Metal	*Concentration of added metal (mg/mL)*	*Residual concentration of active oxygen (%)*
none	none	2
Aluminium	10	2
Chromium	0.1	96
Copper	0.01	24
	0.1	85
Iron	1.0	15
Tin	10	2
Zinc	10	10

[a] The metal-containing H_2O_2 solution was held at 100 °C for 24 h.

Effect of pH on Storage Stability

H_2O_2 solutions are more stable in acidic as compared to alkaline environments. 35% hydrogen peroxide, for which the pH was adjusted, was stored at 100 °C for 6 h, and decomposition ratio of hydrogen peroxide was measured. Example of effects of pH on the decomposition ratio of H_2O_2 was shown in figure 7 (*30*).

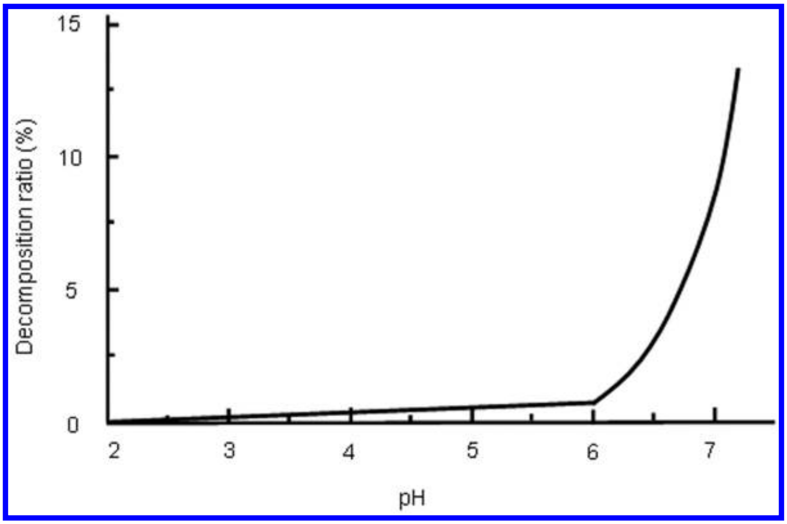


Figure 7. Effects of pH on the decomposition ratio of 35% H_2O_2 heated to 100 °C for 6 h. Reproduced with permission from reference (30). Copyright (1980) The Chemical Society of Japan.

When heavy metals, such as copper, are added to acidic H_2O_2, a baseline decomposition ratio of 2% per year increases by several percent in only a week. However, when the same amount of heavy metals is added to alkaline H_2O_2, decomposition is complete in only a few hours (*29*).

Effects of Surface Activation

The selection of materials of composition for equipment that is used to store or react H_2O_2 solutions are limited. Typically a passivation treatment and a careful cleaning will be required before use. Moreover, this equipment will need to be kept clean so as to not become contaminated with impurities that will catalyze decomposition.

Common steel, copper, copper alloy, and titanium catalyze the decomposition of H_2O_2 solution. Heavy metals, such as silver, lead, platinum, palladium, and mercury, will do so as well and possibly lead to violent decomposition. Materials that are generally acceptable for the use of H_2O_2 solutions are shown in Table X (*29*, *30*, *34*).

Table X. Materials of construction for H_2O_2 solution handling

Types	*Materials*
Metal	Aluminum over 99.6% purity Stainless steel (SUS-304, 304L, 316, 316L) Tantalum Zirconium
Plastic	Rigid polyvinyl chloride Soft polyvinyl chloride Polyethylene Polypropylene Polytetrafluoroethylene Polychlorotrifluoroethylene Polyester
Others	Glass Ceramic

Stabilizers (27, 29)

Generally, to counteract the deleterious effects of trace impurities, a stabilizer is added to H_2O_2 solutions. Many substances have been found for this purpose. Stabilizers typically remove or inactivate impurities that otherwise catalyze the decomposition. Calcined phosphate, fluoride, cyanide, 8-oxyquinoline, and acetanilide form double salts when mixed with heavy metal ions, removing them from solution and in general inactivating them. In addition, precipitated silica, hydrous antimony, and hydrous tin oxide will eliminate trace impurities by adsorption. However, the concentration and impurity profile of the solution to be stabilized may impact the efficiency of these factors and testing is always required to define the amount to add.

If there is a large amount of impurities, the stabilizer content will most likely be insufficient and the desired chemistry must be abandoned. For high-concentration H_2O_2 solutions, stabilizers will usually not work as well. Special conditions are needed to store high concentration H_2O_2.

The stability of H_2O_2 solutions is closely related to purity. To maintain this stability, contamination from impurities must be thoroughly avoided. For example, once removed from its container, a H_2O_2 solution should not be returned to its original container to prevent back-contamination.

Summary of Hazards for H_2O_2 Solutions

30% H_2O_2 can be handled safety by principlely avoiding the obvious sources (e.g. rust) of trace impurities that can catalyze decomposition. A particular danger is from containers bursting as a result of an increase in internal oxygen gas pressure due to decomposition to form oxygen gas. The use of higher concentrations dramatically increases the potential impact of hazards and requires a higher level of concern for storage and use.

pH Management and appropriate material of construction selection are crucial for maintaining the stability of H_2O_2 solutions. If a H_2O_2 solution mixs with combustible substances, the heat generated by its decomposition may cause spontaneous ignition. Therefore, it is important to ensure that H_2O_2 solutions and combustible substances do not come in contact.

When a high-concentration H_2O_2 solution is contacted with certain organic compounds, chances of detonation increase significantly. When handling a 30% H_2O_2 solution, there is less need to be concerned about detonation risks as long as this solution does not become concentrated.

Hydrazine

Hydrazine is a compound of many uses in industry from a fuel to a feedstock. As may be imagined from any compound with a N – N linkage, it is highly reactive. Hydrazine (NH_2NH_2) vapor exhibits decomposition explosively and tends to ignite spontaneously. This strongly reducible inorganic compound is readily oxidized by the oxygen present in air at a low ignition temperature. Moreover, it becomes even more unstable when impurities such as rust are present and porous materials (asbestos, cloth, soil, and wood) absorb it. Upon contact with these materials, the autoxidation of hydrazine vapor is accelerated, potentially leading to spontaneous ignition even at room temperature.

Due to its explosive nature, applications of anhydrous hydrazine are limited to specialized applications such as propellants for rockets. However, hydrazine monohydrate is safer and is more useful as a reducing agent and a raw material in organic synthesis. But dehydration of the hydrate and contamination with initiators can still lead to explosive accidents, justifying our investigation of it prior to use internally.

Hydrazine has been extensively studied, and its spontaneous ignition and explosion risks have been reviewed (*35–38*).

Spontaneous Ignition Risk

The reported minimum ignition temperatures of anhydrous hydrazine and hydrazine monohydrate are listed in Table XI (*35*, *39*, *40*). The trends are clear in that metal surfaces lower the ignition temperature and that anhydrous hydrazine is more sensitive. Note the particularly low ignition temperature for anhydrous hydrazine of 23 °C in the presence of red rust.

Table XI. Minimum ignition or decomposition temperatures for hydrazine as hydrate and anhydrous.[a]

Surface	*Atmosphere*	*Anhydrous hydrazine*	*Hydrazine monohydrate*
Pyrex glass	Air	270 °C[b]	292 °C[b] as 85% hydrazine monohydrate
	Nitrogen	N/A	N/A
Stainless steel (SUS304)	Air	156 °C[b], 164 °C (explosion)[c]	193 °C (spark)[c]
	Nitrogen	No ignition up to 415 °C[b] 531 °C (explosion)[c]	560 °C (ignition)[c]
Iron (Fe)	Air	132 °C[b]	N/A
	Nitrogen	131 °C[b]	N/A
Iron powder (Fe)	Air	N/A	109 °C (spark)[c]
	Nitrogen	N/A	139 °C (ignition)[c]
Black rust (FeO)	Air	N/A	110 °C (ignition)[c]
	Nitrogen	N/A	137 °C (ignition)[c]
Red rust (Fe_2O_3)	Air	23 °C or less[b] 25 °C (explosion)[c]	96 °C (ignition)[c]
	Nitrogen	23 °C or less[b], 25 °C (explosion)[c]	135 °C (ignition)[c]

[a] N/A: Not available. [b] Data from reference (*35*). [c] Original data.

Hydrazine can also decompose violently without the presence of oxygen, forming ammonia, hydrogen and nitrogen gas. Maintaining it under inert gas is a prudent precaution but does not guarantee safe operation. We investigated the effects of material surfaces on the ignition or decomposition temperatures of hydrazine monohydrate using a simple test device for ignition temperature (*41*) (Figure 8) under air or nitrogen atmosphere (Table XI). For both anhydrous hydrazine and hydrazine monohydrate, the spontaneous ignition temperature decreases in the order: glass surface, stainless steel, and iron. Because hydrazine is corrosive to glass, a stainless steel reactor treated with corrosion resistance against hydrazine is more appropriate than a glass-lined reactor for large-scale reactions.

When handling hydrazine monohydrate in a stainless steel reactor, the reactor must be kept under a nitrogen atmosphere. In this situation, the ignition temperature of hydrazine vapor in the absence of a spark is elevated to 560 °C, enabling a safer reaction. If the headspace gas exits the reactor but contains hydrazine vapor and comes in contact with air, the ignition temperature may drop to a dangerous level, below 200 °C. A similar danger occurs if the reactor is placed under vacuum and exterior air is pulled in. Therefore, measures for preventing hydrazine vapor from contacting air under any circumstances are required. If the temperature of the hydrazine-vapor-containing waste gas is high, cooling this gas before emission is prudent to bring it below the ignition temperature.

The presence of iron and rust can reduce the ignition temperature of hydrazine monohydrate below 150 °C, even when under an inert atmosphere. This risk must be managed by careful cleaning and maintainance activities that prevent iron and rust from entering the reactor and peripheral equipment. When using clad steel, in which a thin stainless steel layer is deposited on an iron plate, the existence of pinholes in the stainless steel lining may allow the exterior iron base material to contact the hydrazine vapor possibly leading to the explosive decomposition of the vapor. Careful inspection of such reactors is mandatory prior to the use of hydrazine.

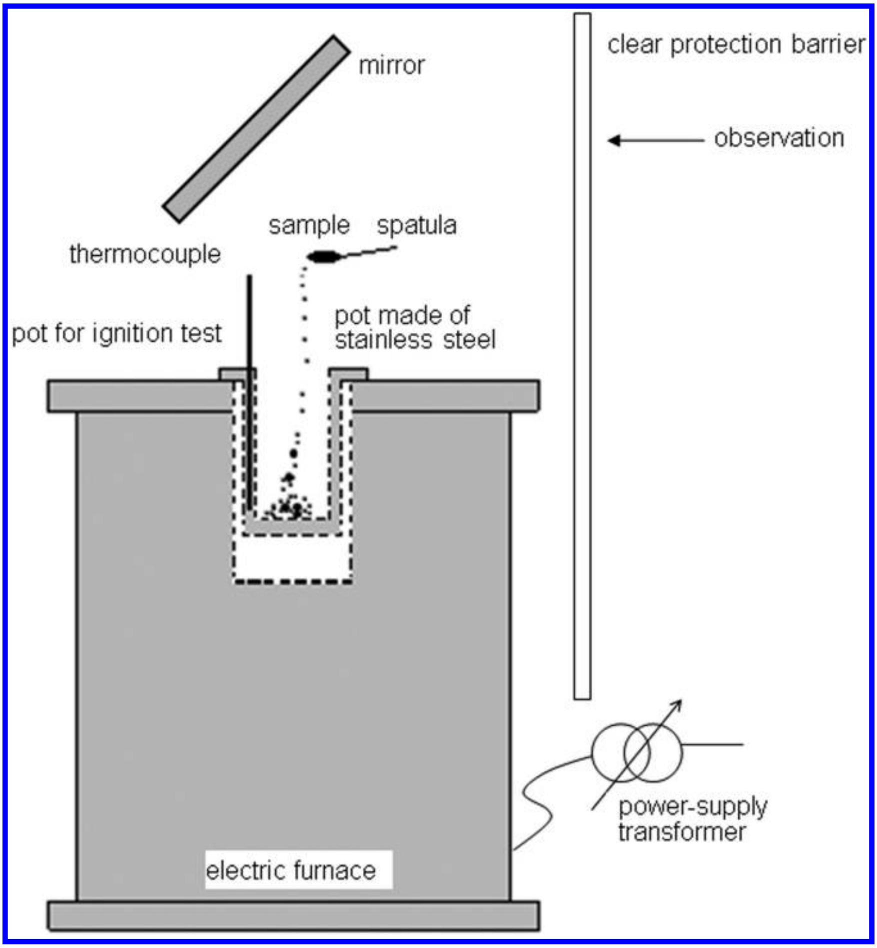


Figure 8. Partial cross-sectional view of Krupp ignition temperature test device

Explosive Decomposition Risks

Hydrazine vapor which has ignited will continue to decompose due to self-heating, even in the absence of air and other oxidizing agents. According to ballistic mortar tests, both anhydrous hydrazine and hydrazine monohydrate have a potential explosive impact 1.4 times as large as that of trinitrotoluene (*35*). Tables XII and XIII list the physical properties of hydrazine (*42–45*) and lower explosive limits of hydrazine vapor, respectively (*35*, *43*).

Table XII. Physical properties of hydrazine

Physical properties	*Anhydrous hydrazine*	*Hydrazine monohydrate*
Melting point	1.4 °C[a]	−51.7 °C[a]
Boiling point	113.5 °C[a]	120.1 °C[a]
Specific gravity	1.021[a]	1.032[a]
Flash point[b]	52 °C (a)[a] 38 °C (b)[c]	73 °C (b)[a] 96 °C (a)[d]
Flash point of aqueous solution of hydrazine[b]	51.2 wt%[e]: 103 °C (a)[f] 38.4 wt%[e]: No ignition point.[f]	

[a] Data from reference (*42*). [b] (a) Cleveland open-cup method; (b) Tag closed-cup method. [c] Data from reference (*44*). [d] Data from reference (*45*). [e] Concentration as anhydrous hydrazine. [f] Data from reference (*43*).

Table XIII. Lower explosive limits of hydrazine vapor[a]

Existing gas	*Lower explosive limit (%)*	*Pressure[b] (kPa)*	*Temperature[b] (°C)*
Air	4.67	101	92−101
Nitrogen	38	101	109−112
Water vapor	30.9	91.9−119	130−135

[a] Reproduced from reference (*35*). [b] Pressure and temperature at the lower explosive limit.

As rust tends to be ubiquitous, the effects of rust on the stability of hydrazine monohydrate were investigated through heating tests using our test tube protocol (Table XIV). When a mixture of red rust and anhydrous hydrazine was heated, the hydrazine vapor decomposed with a explosive sound upon boiling at 125 °C (*46*). In contrast, when hydrazine monohydrate was mixed with iron powder, black rust, or red rust, no ignition or explosion occurred even when heated as high as 220 °C.

Table XIV. Reaction hazards upon mixing hydrazine with metal-based impurities[a]

Run No.	*Hydrazine*	*Impurities*	*Results of observation*
1	Anhydrous hydrazine	Red rust	Explosion[b]
2	Hydrazine monohydrate	Iron powder	No change[c,d]
3	Hydrazine monohydrate	Black rust	No change[c,d]
4	Hydrazine monohydrate	Red rust	No change[c,d]

[a] Original data. [b] The vaporization started at 125 °C. After 330 s, the sample caught fire accompanied with an explosion. The sample temperature increased very rapidly from 115 °C to more than 200 °C. [c] Test conditions: The impurity (1.0 g) was added to hydrazine (2.0 g). [d] Heat was not generated. The sample vaporized at approximately 122 °C.

Various factors such as the generation rate of hydrazine vapor, atmospheric temperature, state of contact with air and rust, and heat release speed, affect the occurrence of ignition. Therefore, those cases which did not display ignition or explosion during these tests should still be evaluated with caution. Compared with anhydrous hydrazine, hydrazine monohydrate is safer.

Conclusions

Every year the chemical industry suffers serious incidents, such as fire and explosion. Considering the large number of plants, laboratories and associated facilities, perhaps the number of these incidents is not particularly large. However, we must strive to reduce these incidents to zero by testing before processing and investigating when we fail. Upon closer examination of the causes, we often find that a specific compound or impurity can be the trigger for an event.

In this study, we investigated hazards arising from an assortment of causes, such as contamination by trace impurities. We also summarized our findings from the literature on these hazards. Still, it is remarkable how convoluted the path to a chemical disaster can be. Thus, from the early stages of bench work, it is important to stretch the limits of our imagination to discover all the possible risks.

To begin the understanding of the conditions that result in these undesirable phenomena, we investigated conditions that can result in ignition, fuming, browning, gas generation, explosion, and rapid increases in temperature, using screening methods which primarily required only readily available Dewar flasks, test tubes, and other general-purpose apparatus. These provided limited but useful information that allowed us to make further decisions on how to proceed.

To make sure appropriately safe conditions are used at large scale, advanced testing should always be conducted, such as the use of various types of reaction calorimetries and accelerating rate calorimetry (ARC) by trained personnel familiar with interpreting the data produced. However, we recommend that our approach using a straightforward screening test is beneficial as an initial feasibility study. Every chemical company examines reaction hazards and assesses safety following a unique protocol. We hope that this chapter describing some of the work flows used at Takeda will be useful for people who are engaged in the assessment of the safety of chemical processes.

Acknowledgments

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Chapter 6

Process Safety in the Large-Scale Manufacture of an Adamantane α-Ketoacid Precursor of Saxagliptin

Joerg Deerberg[*]

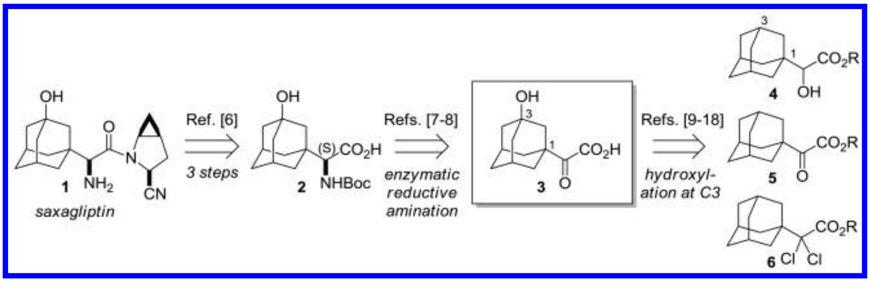
Bristol-Myers Squibb, One Squibb Drive, New Brunswick,
New Jersey 08901-1588
[*]E-mail: Joerg.Deerberg@bms.com

Development of a safe, metric-ton scale batch process for production of a 3-hydroxy-adamantane-1-α-oxoacetic acid, an intermediate in the manufacture of saxagliptin (Onglyza®), presented two key challenges for process safety: A Reformatsky reaction and a bridgehead hydroxylation of the adamantane core using nitric acid. Safety aspects were addressed through detailed examination of operating ranges and thermochemical and mechanism-based risk analysis and mitigation.

Introduction

Saxagliptin **1** (Onglyza®) is a highly potent inhibitor of dipeptidyl peptidase IV (DPP4) for the treatment of Type II *Diabetes Mellitus* (*1–6*). The commercial process for manufacture of **1** (*7*) assembles the principal building block (*S*)-3-hydroxy-adamantylglycine **2** directly from its 3-hydroxy-adamantane-1-α-oxo-acetic acid precursor **3** via enzymatic reductive amination (*8*, *9*) (Scheme 1).

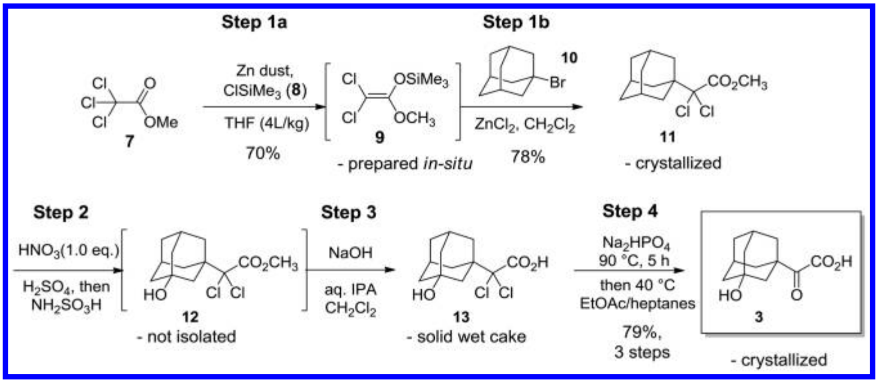
We therefore sought a safe and cost-effective large-scale synthesis capable of producing metric-ton quantities of **3**. Initial approaches starting from adaman-tane α-hydroxy- and α-oxo acetates **4** and **5** (*8*) identified bridgehead hydroxyl-ation at C3 of the adamantane core as the key challenge to a successful bulk synthesis of **3**. Both **4** and **5** were unstable towards a wide range of oxidation conditions (*1*, *10–19*), thus precluding their use on scale. For example, $KMnO_4$ (*1*, *16–18*) as oxidant led to extensive decarbonylation (*20*), producing a mixture of adamantane carboxylates, thus rendering isolation of pure **3** impractical.



Scheme 1. Disconnective scheme for saxagliptin ***1*** *and α-ketoacid precursor* ***3***

The stability issue in the hydroxylation step was ultimately addressed by introduction of *gem*-dichloride substitution in the α-position of adamantylacetic acid, as in **6**. Nitric acid (HNO_3) stood out as the best-performing reagent for oxidation; despite the strongly acidic medium required (*19*), no decomposition of either substrate or product was detected under the reaction conditions.

This discovery led to our eventual manufacturing route for **3** (*21*) (Scheme 2). Therein, Reformatsky reduction of methyl trichloroacetate (MTCA, **7**) in the presence of zinc powder, followed by concomitant *O*-silylation (Step 1a) (*22–24*) yielded α,α-dichloroketene acetal **9** (KTA), which was subjected to Zn(II)-chloride mediated α-*tert.* alkylation (*25*, *26*) with commercially available 1-bromo-adamantane **10**. The resulting product **11** underwent smooth mono-oxidation of the bridgehead position with nitric acid in concentrated sulfuric acid as co-promoter and reaction medium, yielding **12.** Ester hydrolysis provided free acid **13**, which underwent smooth thermal saponification (*27*) of the α-chloro substituents in the presence of mild aqueous base (Na_2HPO_4) at elevated temperature (90 °C) to provide desired **3**.



Scheme 2. Bulk manufacturing route for adamantane α-ketoacid ***3*** *(21)*

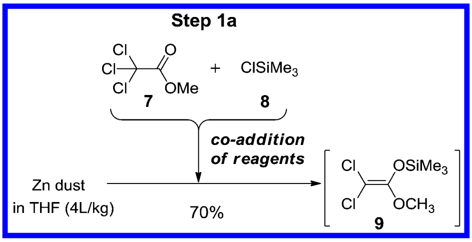
With its attractive overall yields (60-62%, from **10**), inexpensive commercial raw materials, and excellent stability of intermediates, the above route was of interest for use on a manufacturing scale. However, prior to any such application, critical questions regarding the inherent safety of two key transformations were to be addressed: Reformatsky reaction of **7** (Step 1a) and bridgehead hydroxylation of the adamantane core in **11** (Step 2).

Reformatsky Reaction

From the outset, we expected to address questions regarding exotherm control, as well as the activation and eventual safe removal of unreacted zinc powder. In addition, we needed assurances that any reagent accumulation could be detected at an early stage and that effective engineering controls could be implemented to control the exotherm and allow safe stoppage of the reaction at any moment, independent of the degree of conversion and the condition of the batch. To achieve such an *inherently safer design* (*28*), our goal was to identify appropriate layers of protection throughout the process to minimize any residual risks towards safe execution. Each finalized process was to be evaluated by a what-if analysis to ensure core risks and corrective actions were fully defined prior to implementation on scale.

Process Design and Thermochemical Evaluation

As the first safety feature, we adapted *Imashiro*'s protocol (*23*), wherein the two liquid reagents – methyl trichloroacetate (MTCA, **7**, limiting reagent) and chlorotrimethylsilane (**8**, 1.05 equiv) – were added jointly as a homogeneous solvent-less solution from the same reservoir to a suspension of zinc dust (1.5 equiv) in tetrahydrofuran (THF) (Scheme 3). This charge protocol enabled immediate stoppage of reagent flow in the event of issues with reaction initiation or excessive heat generation. A kill switch to the transfer pump allowed for immediate interruption of the reagent addition, should such a need arise. To eliminate the risk of accidental uncontrolled reagent flow, charges were to be made above-surface *via* pump transfer from a reservoir physically located at a level below the main reactor in which the Reformatsky reaction was to take place.



Scheme 3. Reformatsky reaction by co-addition of reagents to zinc slurry (23)

We further studied reaction initiation in the laboratory using a broad range of commercial types of zinc powder. Common procedures for metal surface activation, such as pre-addition of 1,2-dibromoethane (*29*, *30*) or washing of the Zn powder with acid prior to use (*31*), were inadequate in our hands, leading to unreliable initiation patterns and delayed exotherms. Alternate non-chemical activation protocols, such as sonication (*32*, *33*), were deemed impractical on scale. Among the various types of Zn tested, our screen showed that small particle size (<10 µm) was critical to successful initiation of the reaction. Alfa-Aesar type Zn dust (vendor terminology: 'Zn flake'; 1.1 µm particle size; 99.9% metals basis; P/N 13789) performed best and did not require activation. It was therefore chosen for further investigation.

For the choice of reaction solvent, we utilized earlier findings by other research groups that THF was the optimal choice from a reactivity perspective (*22–24*). Stability (*34*) of ketene acetal **9** under the reaction and work-up conditions was adequate for 7-10 h and provided a sufficiently wide window of operation.

On the basis of these reaction conditions, we investigated heat flow using a calorimeter equipped with an *inline* IR probe. Pre-mixed **7** and **8** were slowly charged to a slurry of zinc flake (1.5 equiv.) in THF (4 L/kg) over 100 min using a linear rate of addition. The heat flow plot (Fig. 1, dotted line) showed an initial spike during the initiation phase (8-10 min) as reagent **7**, which accumulated slightly within the first 6% of the addition, became rapidly consumed (Fig. 2). However, as a result of rapid heat dispersion, the spike had no significant effect on the batch temperature (Fig 1, solid line). Following the brief initiation phase, *the ensuing reaction showed complete dose rate-control across a wide range of temperatures* (17-45 °C). *Inline* IR monitoring (Fig. 2) confirmed linear formation of product **9** in lockstep with the addition. Upon complete addition of the reagents, both heat generation and formation of **9** immediately subsided.

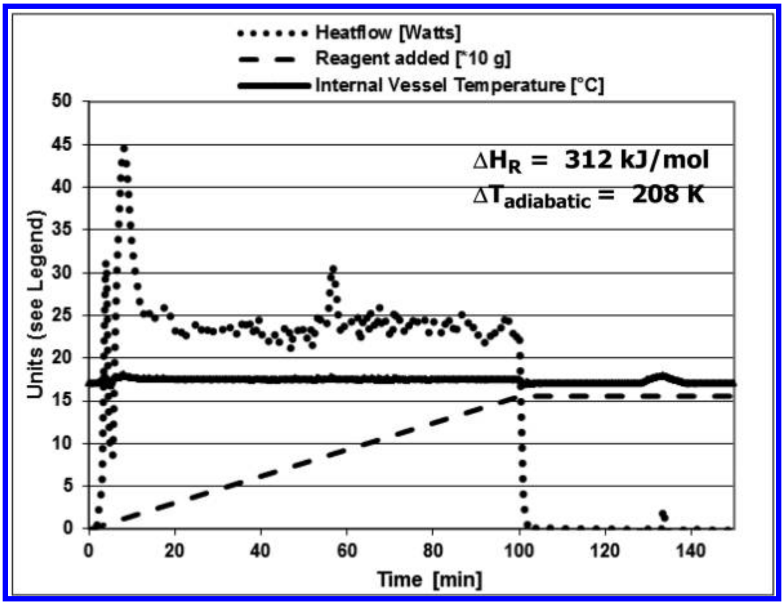


Figure 1. Heat flow during formation of dichloroketene acetal **9** *(0.50 mol scale)*

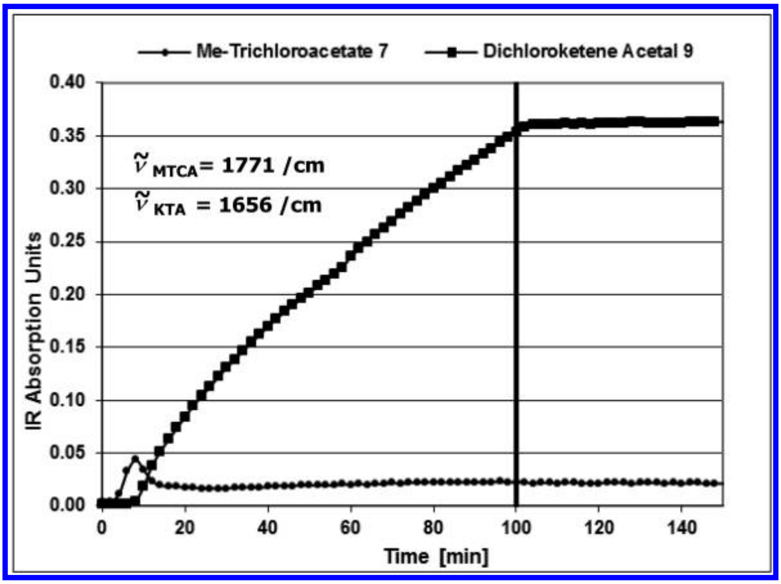


Figure 2. Inline IR Monitoring for formation of ***9*** *(100 min addition time)*

Despite the large adiabatic temperature rise (ΔT_{adia}= 208 K, due to the small heat sink at low volumes), the *observation of dose rate-control provided confidence that the Reformatsky protocol could be used safely on a production scale*, as long as two key engineering controls were in place: co-addition of reagents and *inline* IR monitoring. By contrast, reaction monitoring *via* heat flow alone was deemed inadequate because of the inability to detect reagent accumulation. With a metric-ton scale application in mind, the inertia and inherent slow kinetics of heat transfer through the reactor walls in large systems would lead to a significantly delayed response.

To further assess processing risk, given the large adiabatic temperature rise, we screened for critical parameters that could potentially delay the exotherm. On scale, any such delay could challenge the cooling capacity of the production equipment as the accumulated energy could be released all at once after the reaction engages.

It has long been known that the onset of reactions involving insertion of main group metals into carbon-halogen bonds, such as Grignard (*35–37*) or Reformatsky (*38*, *39*) reactions, is delayed or impeded by the presence of moisture. While the mechanism of this inhibition is not fully understood, the disruption of reactions at the metal surface (*40*) has been reported as a possible cause for the observed retardation.

Indeed, for the present Reformatsky transformation, we observed that even modest levels of moisture or protic contaminants (acids, alcohols, etc.) led to substantial accumulation of methyl trichloroacetate (**7**). In the example below (Fig. 3), using linear reagent addition over 180 min, *moisture contamination of* *the reaction mass (KF=700 ppm) caused a delay in the Reformatsky reaction of approximately 100 min post completion of the addition!* Conversely, dose control was fully restored at moisture levels below 100 ppm, validating the observed dependencies.

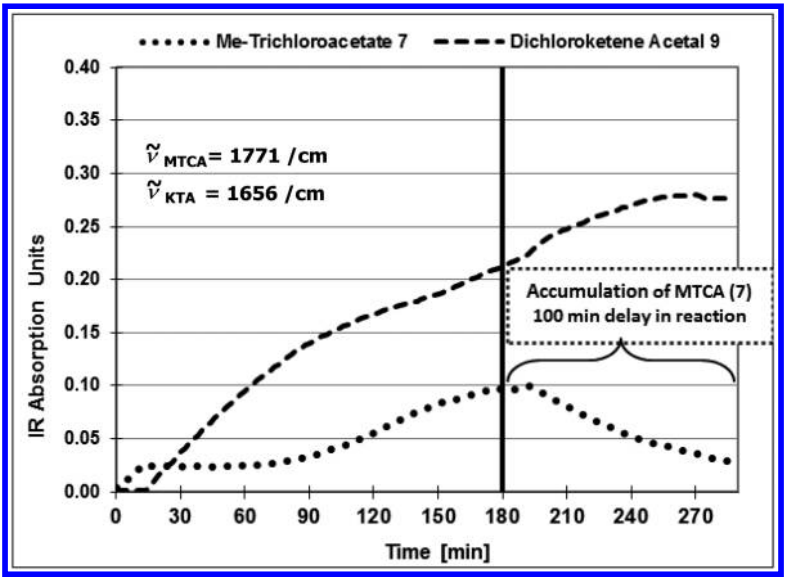
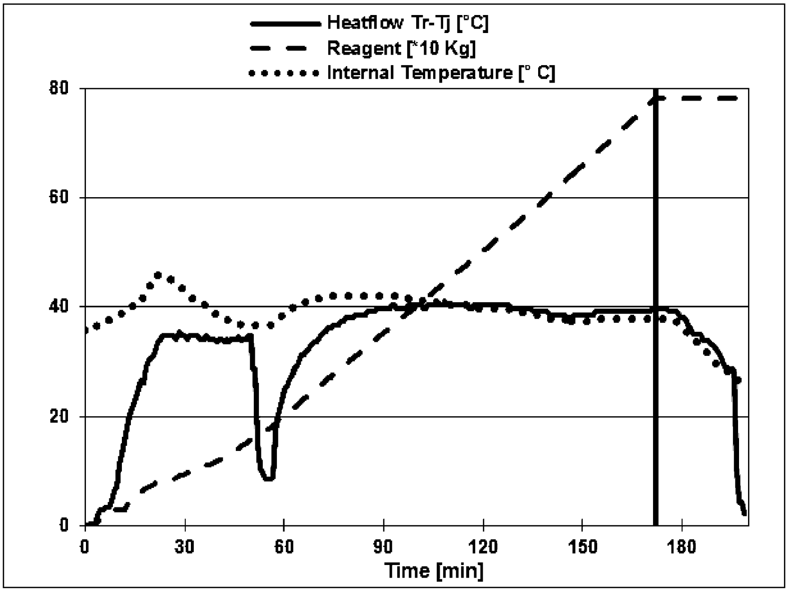


Figure 3. Inline IR - Accumulation of MTCA (7) due to high moisture content of the medium (KF=700 ppm); linear reagent addition (180 min)

Using the precautions outlined above, *i.e.*, calorimetric verification of addition control for the type and lot of Zn powder used, avoidance of protic contaminants, and *inline* IR monitoring, we then confirmed the effectiveness of these measures in the production equipment designated for manufacture of **9**.

Thus, scaling to an inerted 6.3 m^3 size vessel dried to specifications, (i.e., last rinse KF≤100 ppm), a homogeneous solvent-less solution of MTCA **7** (472 kg) and freshly distilled TMSCl **8** (305 kg) were added to a suspension of Zn flake (260 kg; 1.1 µm particle size, 1.5 equiv) in dry THF (1,700 kg; KF ≤ 100 ppm) over 172 min while maintaining the internal temperature between 37-45 °C. Operating the reactor in automatic batch temperature control mode (*41*), we derived heat flow (dQ/dt) by plotting the difference (ΔT) between internal reactor (Tr) and jacket temperatures (Tj) *vs.* addition time (Fig. 4). After a brief initiation period (10-15 min), *inline* IR showed formation of keteneacetal **9** keeping pace with the rate of addition (Fig. 5) (*42*).



Note: The drop in (Tr-Tj) at t=50 min reflects a temporary manual disengagement of jacket cooling in response a batch cooling trend, subsequently compensated by an increase in the addition rate (c.f.: change in slope of dashed graph)

Figure 4. Production run (6.3 m³ vessel) - Heat flow Profile: dQ/dt ~(Tr-Tj)

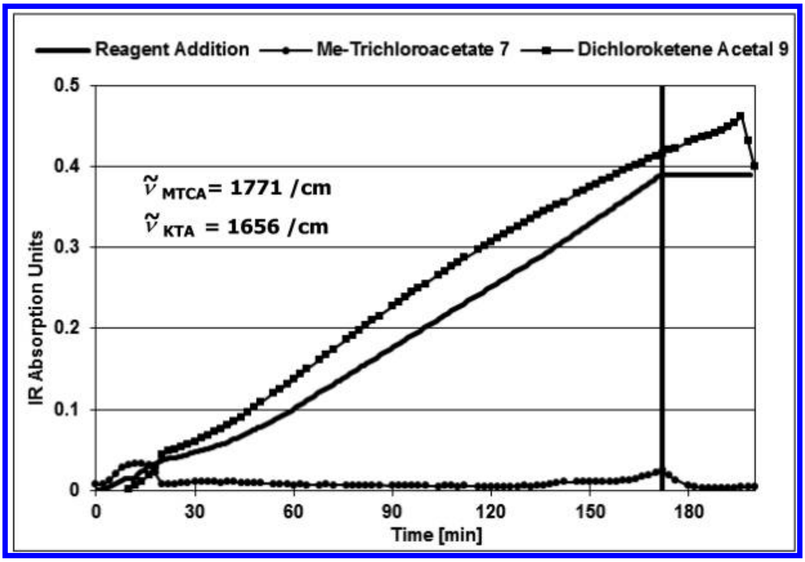


Figure 5. Inline IR Profile - Production run (KF<100 ppm, 172 min addition)

Comparing the heat flow and reaction profiles for small scale (Figs. 1/2) and production runs (Figs. 4/5), any discrepancies observed are attributable to inertia presented by the large-scale equipment, *i.e.*, as a result of a slower heat exchange. The comparison further emphasizes the effectiveness of *inline* IR monitoring as a routine tool to ensure safety of the reduction process on scale.

Reformatsky Reaction: Process Safety and What-If Analysis

With the above process design, any deviation from addition-control can be immediately detected, allowing for proper response times and counter measures to stabilize the process. Table 1 lists a series of potential failure modes, risk factors, and actions to be performed in order to ensure safe processing.

In the event of accumulation of methyl trichloroacetate (**7**), reagent addition is stopped by interrupting the pump charge, leaving sufficient time to respond (15-20 min) before any significant temperature excursion can occur. Whenever addition of the reagent mixture is interrupted, the energy present in the system at any one time is sufficiently moderate that the exotherm *can be allowed to subside safely on its own without external intervention*. As an additional layer of protection, the maximum internal temperature is further limited by the low boiling point of the process solvent (THF, b.p. 66 °C). In this configuration, reagent over- or undercharges have no impact on process safety. If the reagent charge cannot be completed for any reason (e.g., pump failure, cooling failure, power failure, poorly controlled exotherm, etc.), the batch remains in a stable and contained state, even if no further actions are taken. Irrespective of how much of the reagent charge has been completed, the mass can at any point be drained directly to a *Nutsche* or bag filter to recover excess unreacted zinc. Subsequent downstream processing is then performed on the filtrate rich in ketene acetal **9**.

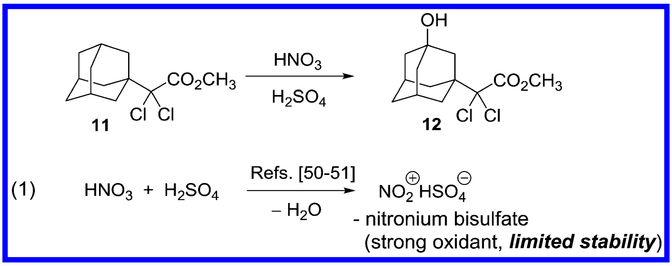
Overall, *Reformatsky* reaction of methyl trichloroacetate has enabled safe, efficient, and cost-effective access to high-quality dichloroketene acetal **9** through a process based on an *inherently safer design* (*28*).

Adamantane Bridgehead Hydroxylation

The second step of focus in the synthetic sequence leading to **3** from a hazards control perspective was C3-hydroxylation of **11** (Scheme 4). Early screening established the superiority of nitric acid (HNO_3) (*19*) over other oxidants (*vide infra*) (*1*, *10–18*). Among a number of conditions and acid additives tried, neat concentrated sulfuric acid (96–98 wt-%) was the most effective co-promoter for the oxidation (*43*). In the original laboratory procedure (*21*), portionwise addition of solid **11** to a cold (0–5 °C) mixture of HNO_3 in concentrated H_2SO_4 resulted in clean formation of desired alcohol **12** in near-quantitative yield (95–98%).

Table 1. What-iIf Analysis for *Reformatsky* Process

What if...	***Risk***	***Risk control features (engineering or procedural)***	***Safety Action***
Uncontrolled reagent addition	Runaway reaction	Slow reagent charge *via* pump from reservoir located below main reactor	No further action required
Over/undercharge	No safety impact	Recalculate downstream charges if necessary	No action required
Agitator failure	Uneven heat dissipation	Agitating action provided by high-velocity pump-around loop	No action, depending on pump loop turn-over frequency
Cooling failure *OR* Failure of IR monitor or loop	Overheating; Product quality	Co-addition of MTCA/ TMSCl prevents significant reagent accumulation at any given time	Stop reagent pump charge via kill switch; Resume when systems are restored or send mass to filter
High moisture levels in solvent	Heat accumulation	KF moisture analysis of purchased solvent and final equipment train rinse	Reject solvent batch(es); Repeat equipment rinse
Protic impurities in TMSCl	Heat accumulation	Mandatory distillation of reagent before use	No further action or testing required
Performance/ quality issues with Zinc flake	Heat accumulation	Qualify through use test in calorimeter (→ dose control)	Repeat for each new vendor/lot
Batch deviation from dose control	Heat accumulation	Continuous IR monitoring	Stop reagent addition and send mass to filter
General power failure	Heat accumulation	Self-limiting design controls exotherm through auto-stop of reagent pump charge	No further action; Resume process-ing when restored



Scheme 4. Bridgehead hydroxylation of ***11*** *with nitric acid*

Process Design

Upon further examination, solid addition of **11** was not amenable to scale-up due to a large amount of heat generated during the reaction; reactor temperature excursions of >30 °C were difficult to avoid. Moreover, the combination of HNO_3 with concentrated sulfuric acid (commonly referred to as '*mixed acid*' or '*nitrating acid*' (*44–46*)) presented challenges from a safety and operational perspective. Preparation of the reagent is highly exothermic and requires diligent engineering controls to prevent thermal runaway reactions (*47*). Even in the absence of organic substrates, *nitrating acid* mixtures are reported to have limited thermal stability (*48*) and display strong nitrating and oxidizing properties (*49*, *50*).

Based on the pioneering work by *Ingold* et al. (*51*, *52*), such mixtures are known to generate nitronium bisulfate ($NO_2^+HSO_4^-$) as the active agent (Scheme 4, Eq. 1). Accidental contact with incompatible organic substances can result in fires or explosions. For example, *nitrating acid* cannot be combined with most organic solvents (*e.g.*, acetone, acetonitrile, lower alkyl alcohols, dichloro-methane, DMSO, aromatic hydrocarbons), presenting further challenges to process development.

Another potential complication with the use of this oxidant is generation of nitrous gases (NO_x) and formation of nitrate esters from alcohols. Such esters are frequently thermally labile; in extreme cases, especially with low molecular weight alcohols or polyols, these esters can have explosive properties (*53*, *54*). In acidic media, nitrate esters exist in equilibria (*55*, *56*) with the corresponding free alcohols and nitric acid, giving rise to redox reactions and potential evolution of NO_x. In a condensed phase and in presence of sensitive organic matter, such gases can pose risks to process safety due to their oxidizing properties (*57*); Moreover, NO_x are highly toxic, regulated pollutants that require strict exposure controls (*58*). Overall, to achieve an intrinsically safer process design, the formation of NO_x and nitrate esters should be avoided.

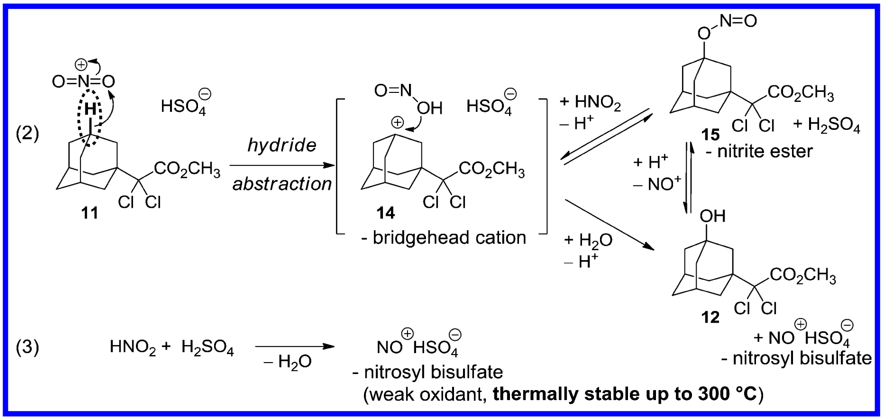
Addressing potential processing issues, we found that the initial pre-mixing of mineral acids was unnecessary. Indeed, slow addition of a stoichiometric quantity of aqueous 50–70 wt-% HNO_3 (1.05 equiv) to a suspension of **11** in concentrated H_2SO_4 at 5–10 °C produced adamantanol **12** in near-quantitative yield within 2 h while significantly improving the exotherm control over the original solid addition protocol. As a safeguard against uncontrolled reagent addition, the risk of accidental overheating was effectively controlled by slow charge of aqueous nitric acid *via* pump from a reservoir located below the main reactor. A kill switch to the pump allowed for immediate interruption of the HNO_3 charge in the event of a temperature excursion.

The clean reaction profile and ability to limit the HNO_3 oxidant charge to a stoichiometric amount effectively eliminated the risk of nitrate ester formation to non-detectable levels (*59*, *60*). Likewise, no gas evolution or discoloration was observed. Both substrate **11** and product **12** showed no sign of degradation under these conditions, even at elevated temperatures up to 40 °C for over 24 h.

At this stage, two aspects remained to designing a safe hydroxylation process: identification of a suitable quench protocol and extraction of the product with a compatible organic solvent.

Ideally, an effective quench would remove any remaining oxidizers from the crude reaction mass, regardless of the degree of conversion. To identify the reactive components present during and after the reaction, a mechanism-based risk analysis was performed.

Based on reports by *Olah* et al. (*61*, *62*), adamantane hydroxylation with nitric acid proceeds *via* nitronium ion-induced selective hydride abstraction at the bridge-head carbon, giving rise to an adamantyl cation, such as **14** (Scheme 5, Eq. 2). From the observed reaction stoichiometry with **11** and near-quantitative yield of **12**, mass balance at full conversion generates one molar equivalent of nitrosyl bisulfate as by-product. This commercially available reagent (*63*) is formed by reaction of nitrous acid with concentrated sulfuric acid (Eq. 3). Unlike the corresponding nitronium salt, nitrosyl bisulfate is known to be thermally stable up to 300 °C (*48*). However, as an industrial diazotization reagent, it still retains oxidizing properties.



*Scheme 5. Mechanism of bridgehead hydroxylation of **11** with nitric acid*

To encompass the need for a safe work-up, even in the event of an incomplete reaction or an accidental overcharge of nitric acid, the desired quench protocol would need to eliminate reactive nitrogen species at both the *N*(III) and *N*(V) oxidation states.

We thus introduced sulfamic acid (H_2NSO_3H) as the reductant of choice since it possesses the requisite properties. Specifically, sulfamic acid is known to *react rapidly* with both *nitrosyl* (NO^+) (*64*, *65*) and *nitronium* (NO_2^+) (*66*) species under acidic conditions (Eqs. 4 and 5), generating equimolar amounts of sulfuric acid and inert gases (N_2 and N_2O (*67*), respectively).

$$(4) \quad \underset{\text{- sulfamic acid}}{H_2NSO_3H} + NO^+ \xrightarrow{\text{Refs. [63-64]}} N_2\uparrow + H_2SO_4 + H^+$$

$$(5) \quad H_2NSO_3H + NO_2^+ \xrightarrow{\text{Ref. [65]}} N_2O\uparrow + H_2SO_4 + H^+$$

For comparison, reduction of nitrite/NO^+ with sulfamic acid has been shown to proceed two orders of magnitude more rapidly than the equivalent reaction with urea (*64*), a frequently used reductant for processes involving nitrous acid. Urea, in turn, is virtually unreactive towards nitrate/NO_2^+ (*68*) and was therefore not pursued for our purposes.

Employing 5 wt % aqueous sulfamic acid in the quench protocol, all residual oxidants were readily removed. Extraction of reaction product **12** from the resulting aqueous suspension with an acid-resistant organic solvent (e.g., dichloromethane) obviated the need for neutralization of excess acid, thereby keeping process volumes and overall waste generation low (V_{max} < 20 L per kg of **11**).

Thermochemical Evaluation and Final Procedure

Prior to implementing the hydroxylation process on scale, reactive hazards were evaluated quantitatively by calorimetry. In addition, a what-if analysis was conducted to ensure residual processing risks were appropriately identified and principles for an inherently safer design were incorporated.

Differential Scanning Calorimetry (DSC) showed excellent thermal stability of both substrate **11** and reaction product **12** (Table 2).

The heat of reaction was determined for both the oxidation and the reductive quench (Table 3).

Due to a large adiabatic temperature rise, the addition of nitric acid requires efficient cooling and a slow charge. *Gas evolution measurements confirmed the absence of nitrous gases.*

Thermal stability of the crude mass after reaction completion was assessed using the Advanced Reactive System Screening Tool (ARSST). Samples were prepared in a test cell pressurized to 300 psi with nitrogen. The temperature was ramped from room temperature to 175 °C at 1 °C/min. Stability of the stream was excellent, with only minor self-heating events (Table 4).

Table 2. Thermal stability of starting material and product

Compound	*Endotherm (°C)*	*Exotherm (°C)*
Starting material (**11**)	79.7 (melt)	308 (decomp.)
Hydroxylation product (**12**)	117 (melt)	–

Table 3. Reaction enthalpy for bridgehead hydroxylation of 11[a]

Process Step	*ΔH_R [kJ/mol]*	*$\Delta T_{adiabatic}$ [°C]*
Addition of 60 wt-% aqueous nitric acid	–70.8	+102
Quench into 5 wt-% aqueous sulfamic acid	–390.5	+35

[a] Notes: Compared to the quench, heat capacity during addition of nitric acid is lower due to smaller process volumes, resulting in a larger adiabatic temperature rise.

Table 4. Thermal stability of reaction mass

Process	*Onset Temp. (°C)*	*Self-heating Rate (°C/min)[a]*
Crude mass post reaction completion and prior to workup	40	3
Same as above	125	5

[a] Note: The two self-heating events shown above were considered minor and do not pose a safety risk, even in the event of a significant temperature excursion (e.g., ΔT of 50 °C above the 20 °C target temperature). However, a quality risk to the product **12** is incurred above a vessel temperature of 40 °C.

From this assessment, the oxidation is safe to run in typical corrosion-proof processing equipment (glass, Hastelloy C22) with minimal engineering controls. Formation of potentially hazardous nitronium salts is avoided by slow addition of nitric acid, which reacts rapidly and stoichiometrically with the substrate. To avoid evolution of hazardous nitrous gases during work-up, the reaction mass is quenched into dilute aqueous sulfamic acid. This treatment ensures complete reduction of residual nitrosyl/nitrite and nitronium/nitrate species to innocuous nitrogen or dinitrogen oxide gas, respectively.

With the above design features, the finalized hydroxylation process was performed as follows:

Table 5. What-if Analysis for Adamantane Hydroxylation Process

What if...	*Risk*	*Risk control features (engineering or procedural)*	*Action*
Uncontrolled reagent addition	Runaway reaction	Slow reagent charge *via* pump from reservoir located below main reactor	No further action required
Reagent overcharge	Emission of reactive NO_x	Absence of organic solvents; Sulfamic acid scrubber with constant stream of nitrogen gas through headspace; 50% Excess sulfamic acid built into work-up protocol	Proceed to work-up (eliminates oxidants, incl. NO_x)
Reagent undercharge	Product quality	No safety implications	Charge additional reagent as needed
Cooling failure *OR* Agitator failure	Overheating; Product quality	Slow reagent charge *via* pump	Stop reagent pump charge *via* kill switch; Resume when systems are restored or send mass to quench tank
General power failure	Heat accumulation	Self-limiting design controls exotherm through auto-stop of reagent pump charge	No further action; Resume process-ing when power is restored

To a cold (5–10 °C) suspension of **11** (255.0 kg; 0.92 kmol) in 96% sulfuric acid (1,403 kg; 5.5 kg/kg of **11**) was added 60 wt-% nitric acid (102 kg; 0.97 kmol; 1.05 equiv) below 10 °C *via* pump charge over 1 h. Agitation was continued at 10–15 °C for 90 min, resulting in a clear solution. The reaction mass was analyzed for completion by HPLC (criteria: $\leq$ 0.5 area-% **11**). The viscous reaction mass was slowly quenched into a solution of sulfamic acid (132.6 kg; 1.38 kmol; 1.50 equiv) in water (2,500 kg) while maintaining the internal temperature below 15 °C. Dichloromethane (1,600 kg) was added to the resulting oxidant-free white slurry and the organic (bottom) phase was transferred to a separate vessel. The remaining aqueous (top) layer was re-extracted with dichloromethane (850 kg) and the organic (bottom) extracts were combined and washed with 10% brine solution (1,375 kg) until pH > 4.0. When the wash pH passed specification, the organic extracts were concentrated under slight vacuum below 40 °C to approx. 650–750 L of total volume. The rich concentrate containing **12** (264.1 kg; 0.90 kmol; 98% yield) was directly introduced into the next step (ester hydrolysis).

Adamantane Hydroxylation: What-If Analysis

In the final process, key design features, such as exotherm control, the absence of incompatible solvents, and avoidance of nitrous gases have been incorporated. With stability risks absent under normal processing conditions, attention was focused on potential parameter excursions and failure paths (Table 5).

If the reagent charge cannot be completed (e.g., pump failure, cooling failure, power failure, poorly controlled exotherm, etc.), the batch remains in a stable state, even if no further actions are taken. Irrespective of the degree of conversion, and in the event of an accidental overcharge of nitric acid, the reaction mass remains stable and can at any point be quenched into an excess of aqueous sulfamic acid solution, thus eliminating all oxidative species or gases.

While nitrous gases are not formed in the process, as an additional layer of protection, the equipment headspace was continually purged with nitrogen and exhaust lines directed to a scrubber containing dilute aqueous sulfamic acid.

Conclusions

Manufacture of saxagliptin precursor 3-hydroxy-adamantane-1-α-oxo-acetic acid (**3**) was enabled through a 4-step synthesis starting from inexpensive 1-bromo-adamantane.

The present contribution describes examination of two critical process steps for risk factors with potential impact on operational safety: Reformatsky reduction of methyl trichloroacetate (MTCA) using elemental zinc and selective bridgehead hydroxylation of the adamantane core with nitric acid.

Safety aspects were evaluated through detailed thermochemical and mechanism-based risk analysis. Risk mitigation was achieved through a self-limiting design, incorporating effective engineering controls that ensure stable batch processing under a variety of planned and unplanned operating conditions, including partial and complete system outages. Key design features are controlled pump charges of reagents from reservoirs located below the main reactors, preventing accidental siphoning, and the ability to safely proceed to work-up at any time during the process, irrespective of the degree of conversion or reagent over-/undercharges. Potential failure paths were identified and mitigated through what-if analyses.

The resulting processes were successfully applied to the commercial manufacture of 3-hydroxy-adamantane-1-α-oxo-acetic acid (**3**) on a metric-ton scale.

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Chapter 7

Thermal Risk Assessment: A Powerful Tool for Route Selection for Scale-Up Applied to Diels–Alder Reactions

Stefan Abele,[*,1] Gunther Schmidt,[1] Jacques-Alexis Funel,[1]
Mischa Schwaninger,[2] and Sven Wagner[2]

[1]Process Research Chemistry, Actelion Pharmaceuticals Ltd, Gewerbestrasse 16, CH-4123 Allschwil, Switzerland
[2]Swissi Process Safety GmbH, Mattenstrasse 24, CH-4002 Basel, Switzerland
[*]E-mail: stefan.abele@actelion.com; Telephone: +41 61 565 67 59

The thermal risk assessment of the Diels–Alder reaction of acetoxyacrylonitrile, acrylonitrile, and chloroacrylonitrile with the diene (cyclohexa-1,5-dien-1-loxy)trimethylsilane (**1**) is presented. Starting with the conceptualization of the problem, a step-by-step approach serves as an example for a sound and systematic evaluation of risks. A holistic view of the relevant data ranging from thermokinetics, storage, availability, costs, and throughput shows that the choice of a safe route is a multi-dimensional task. In a second part, a novel synthesis of spiro[2.4]hepta-4,6-diene **6** is described. This highly reactive diene has a large thermal potential. A systematic thermal stability study of both the reaction mixture and the product led to recommendations for safe processing, including the highly exothermic synthesis and the distillation. In both cases, the safe processing of hazardous chemistry at the tolerated scale was pivotal for the expeditious delivery of material for the production of API (Active Pharmaceutical Ingredients).

Keywords: Diels–Alder; dienes; dienophiles; assessment of thermal risk; Stoessel criticality diagram; DSC; reaction calorimetry; runaway; hazardous reactions

"The person who goes farthest is generally the one who is willing to do and dare. The sure-thing boat never gets far from shore."— Dale Carnegie (1888–1955)

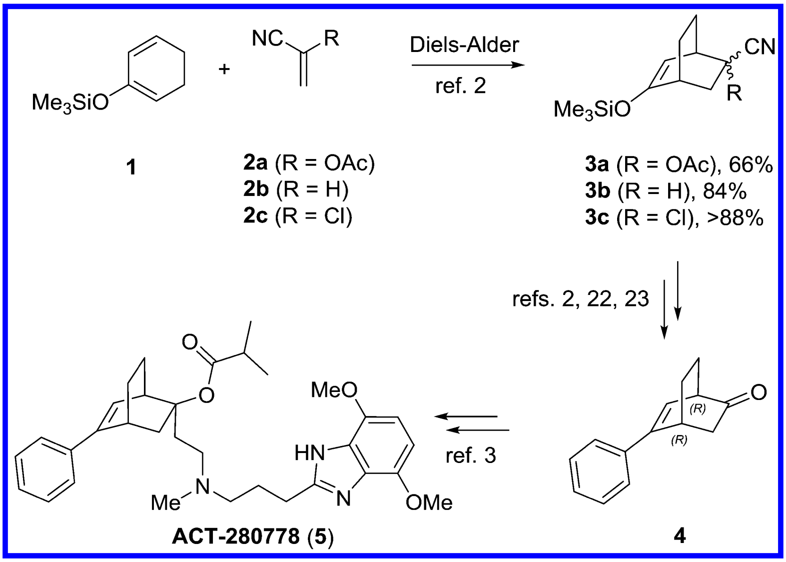
Introduction

Highly exothermic reactions and hazardous operations pose a major challenge to process chemists in the pharmaceutical industry whose honorable task is to find safe and robust routes to deliver material for preclinical and clinical studies in the shortest time possible. Hazardous reactions can be seen either as a roadblock or as an opportunity. Clearly, the risks associated with thermal runaway reactions have to be seriously assessed and might block certain synthetic routes. In fact, the *primary mandate during scale-up* is to develop processes that are safe to the coworkers, to the environment, and are under control. On the other hand, hazardous reagents or reactions sometimes possess the potential for significant shortcuts, thereby saving significant time–a major goal during drug development where early critical milestones (for example a clinical proof of concept) are important. Hence, if hazardous chemistry is handled in a safe manner, the above mentioned challenge can be transformed into an opportunity.

In the following sections, we present a discussion of the risk assessment of several highly exothermic Diels–Alder reactions and their hazard management that rendered them viable processes on large scale (*1*). The suitability of three acrylic monomers, acetoxyacrylonitrile (**2a**), acrylonitrile (**2b**), and chloroacrylonitrile (**2c**) as dienophiles in the Diels–Alder reaction with (cyclohexa-1,5-dien-1-yloxy)trimethylsilane (**1**) is discussed (Scheme 1) (*2*). The Diels–Alder products (**3**) are precursors for the synthesis of the enantiomerically pure bicyclic ketone **4** that is the pivotal intermediate for the synthesis of an Active Pharmaceutical Ingredient (API), the L/T-channel blocker ACT-280778 (**5**) (*3*). The choice of the route used for scale-up (> 100 kg) is rationalized in a step-by-step fashion, considering availability, cost, processing time, and temperature, in addition to the safety aspects.

Expanding diversity of libraries for screening is a current challenge in Medicinal Chemistry (*4–6*). The diene spiro[2,4]hepta-4,6-diene (**6**, Figure 1) serves this purpose as a versatile and reactive Diels–Alder diene for the synthesis of tricyclic building block **8** with four sites of functionality (two ester functions (R_1 and R_2), a double bond, and a cyclopropyl ring) (*7*). The syntheses of **6** from cyclopentadiene (Cp) were not deemed scalable. A novel process is described that allows to scale up the batch reaction. Inasmuch as the thermal potential of this diene was found to be very high, much work was required to assure safety at the scale we desired to achieve and this triggered in-depth thermokinetic studies. We present here a case study of how to approach hazardous reactions, reagents and work up protocols as a real life lesson of how scientists and engineers should proceed in such a situation.

The second half of this chapter is devoted to the synthesis and thermal risk assessment of **6** that was decisive for an early choice of the desired downstream route.



*Scheme 1. Diels–Alder reactions used for the synthesis of ACT-280778 (**5**).*

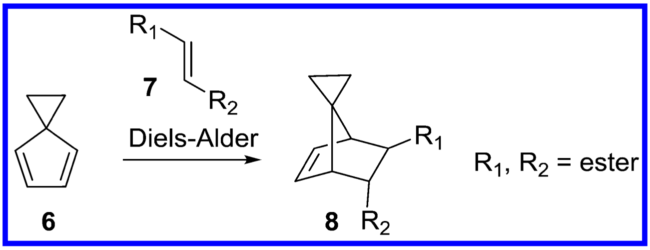


*Figure 1. Spiro[2,4]hepta-4,6-diene (**6**) as substrate for Diels–Alder reactions leading to versatile bicyclic core structures **8**.*

Safety Assessment of Acrylic Dienophiles 2 for the Diels–Alder Reaction with (Cyclohexa-1,5-dien-1-yloxy)trimethylsilane 1

Acrylonitrile and its derivatives are known to polymerize exothermically. Generally, polymerization of various types of alkene monomers has been shown to be the major cause for runaway reactions in a study of 134 incidents from 1962–1997 (*8*). Therefore, acrylonitriles and other active alkene monomers are typically mixed with stabilizers for safe shiping and storage (*9*, *10*). It is important to note that the stabilizers have been optimized for the neat monomers and can be deactivated or decomposed by the reaction partners (*vide infra*). In addition, physical operations like distillations might deplete the stabilizer in the mixture or separate the monomer from the stabilizer. Besides the risk of the exothermic polymerization of these dienophiles (**2**), a thorough risk assessment has to consider the highly exothermic Diels–Alder reaction (two sp^3–sp^3 carbon bonds are formed), and the stability of the Diels–Alder product **3** (*11*). Such a safety assessment was crucial for the rapid selection of a suitable route for the production of >180 kg of the bicyclic intermediate *rac*-**4**, as alternative approaches were not available at that time.

Incidents during chemical reactions arise from the thermal instability of the chemicals and mixtures, from heat generation of the synthesis reaction, and from gas evolution. To properly address the impact of the thermal risk of a process, these hazards need to be correlated with the severity of an incident and the probability of its occurrence. The so-called cooling failure scenario is a good means to challenge the process design and assess the thermal risk (Figure 2) (*13*).

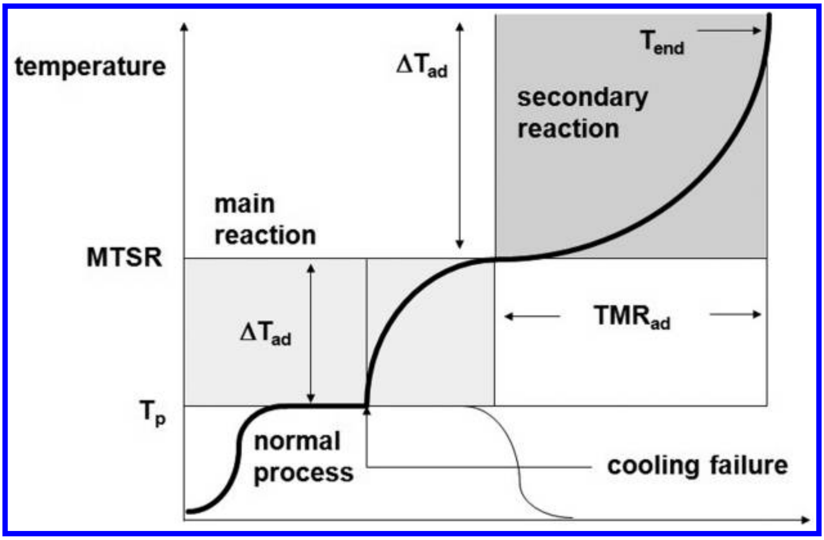


Figure 2. Cooling failure scenario as stress-test for the process.

The typical order of the minimally required thermal safety experiments to gather the relevant parameters is described in the following:

(1) Thermal stability of the product mixture:

a. The severity (*12*) is screened by DSC (Differential Scanning Calorimetry) measurements to uncover the thermal potential which gives the maximum self-heating potential ΔT_{ad} (adiabatic temperature raise) of the decomposition (secondary) reactions.

b. The probability of this self-heating to occur can be estimated using a time scale. If there is enough time left to implement effective emergency measures before the decomposition reactions become too fast after a cooling failure, the probability of such a runaway will remain low. The probability of a runaway can be derived from thermokinetic data, e.g. the onset temperature (in the context of thermal process safety, the onset temperature is the temperature where the equipment first detects the heat generation of the peak, i.e. left temperature limit of the peak. This should not be confused with the "onset temperature" reported in most scanning calorimeters which is used for the determination of phase transfers, e.g. melts) or a series of isothermal or dynamic DSC experiments, either via simple Arrhenius plots or AKTS modeling (*13*, *14*). The output is the TMR_{ad}, (time to reach the maximum rate of decomposition due to self-heating of the material under adiabatic conditions).

(2) Synthesis reaction: for the desired reaction, reaction calorimetry by RC1 (bench scale heat flow calorimeter from Mettler-Toledo) yields the MTSR (maximum temperature of the synthesis reaction), the maximum heat flow, the total heat released by the desired reaction, and the degree of accumulation (*15*) during dosage. In the case of a cooling failure, the TMR_{ad} at MTSR determines if there is still enough time for emergency measures to shut down the reactor before disaster.
(3) Gas evolution: mass transfer issues like release of gases through the vent lines and foaming must and were taken into account in this assessment.

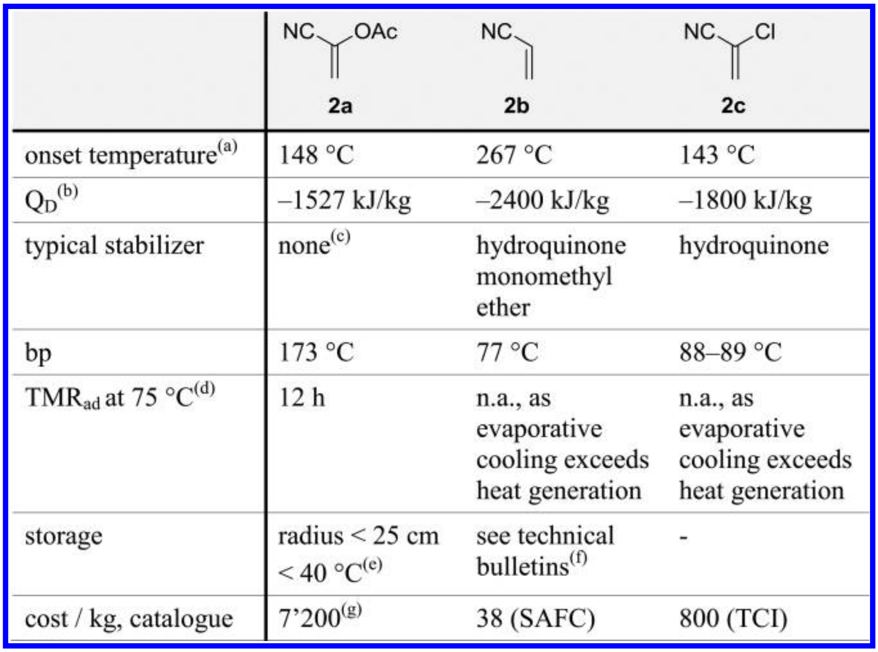
This assessment was performed with both the Diels–Alder reagents and with the respective reaction mixtures, and the results are summarized in Tables 1 and 2, respectively. The goal of the following chapters is to summarize the process of risk assessment, based on published experimental data (RC1 data, DSC and C80 thermograms, and kinetic modeling curves) (*11*).

Properties of the Dieneophiles

The diene **1** posed less hazard potential: the DSC of **1** under argon in the presence of 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) showed an onset of 100 °C with a decomposition energy $Q_D = -287$ kJ/kg. When measured in air, an additional exotherm starting at 76 °C was observed (–20 kJ/kg), indicative of a potential oxidation of the TMS-ether. The DSC traces of all three dienophiles (Table 1) show–as expected–very high energies that would lead to an adiabatic temperature rise of > 750 K. Considering the process temperatures for the intended Diels–Alder reactions of 83–140 °C (vide infra, Table 2), in comparison with DSC onset of the product mixtures, the 100-K rule (rule of thumb saying that 100 K below the DSC onset temperature there will be "no risk" of hazardous self-heating) is clearly violated for dienophiles **2a** and **2c**. For dienophiles **2b** and **2c**, their boiling represents an additional safety barrier; the *O*-acetyl dienophile **2a** decomposes before boiling. Whereas **2b** and **2c** are readily available commodity chemicals, **2a** is a compound that needs to be custom made with long lead times. Several kilograms of **2a** were required for the first Diels–Alder reactions (*2*), so the conditions for safe distillation and storage had to be estimated. Isothermal DSC's were used for the Arrhenius plot that allowed to estimate the $TMR_{ad} = 12$ h at the intended jacket temperature 75 °C for the vacuum distillation of **2a**. The Frank-

Kamenetskii approach was used based on several isothermal DSC experiments (*16*). This led to quite stringent requirements for the storage of **2a**. Of the three dienophiles acrylonitrile **2b** is by far the least expensive. Based only on the aspects presented in Table 1, acrylonitrile **2b** would be the preferred dienophile.

Table 1. Key data of the three dienophiles 2



	2a	2b	2c
onset temperature[(a)]	148 °C	267 °C	143 °C
Q_D[(b)]	–1527 kJ/kg	–2400 kJ/kg	–1800 kJ/kg
typical stabilizer	none[(c)]	hydroquinone monomethyl ether	hydroquinone
bp	173 °C	77 °C	88–89 °C
TMR_{ad} at 75 °C[(d)]	12 h	n.a., as evaporative cooling exceeds heat generation	n.a., as evaporative cooling exceeds heat generation
storage	radius < 25 cm < 40 °C[(e)]	see technical bulletins[(f)]	-
cost / kg, catalogue	7’200[(g)]	38 (SAFC)	800 (TCI)

[a] DSC of dienophiles as received from suppliers. [b] Q_D: decomposition energy, < 0 kJ/kg means exotherm. [c] The onset temperature of **2a** in the presence of 0.05% 2,6 di-*tert*-butyl 4 methyl phenol (BHT) was lowered to 128 °C with a similar $Q_D = -1588$ kJ/kg. [d] 75 °C is the wall temperature during the distillation of **2a** under reduced pressure. T_{D24} (temperature at which TMR_{ad} = 24 h) was 64 °C. [e] In a cylindrical container, based on Frank-Kamenetskii approach, using the power and activation energy from the Arrhenius plot for the decomposition of **2a**. [f] **2b**: Ineos, safe storage and handling guide. [g] Custom synthesis offer, 5 weeks delivery time.

Thermokinetic Experiments To Guide the Selection of the Best Dieneophile

Next, the Diels–Alder reactions of **2** and **1** were studied by DSC and reaction calorimetry (Table 2). The low-cost acrylonitrile **2b** was deprioritized for the development as an additional chlorination step had to be added before releasing the ketone function in **4**, making this dienophile less attractive from a processing point of view, as compared to the ketene equivalents **2a** and **2c**.

Table 2. Key data of the Diels–Alder reaction of the three dienophiles 2 with the diene 1 (see Scheme 1).

	2a + 1	*2b + 1*	*2c + 1*
onset temperature[a] Q_R/Q_D[b]	68 °C ∑ –803 kJ/kg	72 °C ∑ –387 kJ/kg	64 °C/202 °C –341/–539 kJ/kg
peak temperature reaction	184 °C	167 °C	131 °C
reactivity	low (neat)	medium (neat)	medium 34% w/w in toluene
T_p / t[c]	140 °C/24 h	83 °C/24 h	100 °C/20 h
MTSR (RC1)	245 °C neat	n.a.	132 °C 34% w/w in toluene
TMR_{ad} at MTSR[d]	40 min	n.a., as evaporative cooling exceeds heat generation	> 800 h
largest batch size	1–2 kg glass flask	100 g glass flask	54–147 kg 434 kg **3** produced 200-L steel reactor

[a] DSC of the mixtures of dienophile **2** and **1**. Catalytic amounts of TEMPO were added to the reactions with **2b** and **2c**. [b] Q_R: energy of the desired reaction (1st event), Q_D: decomposition energy (2nd event). If not separated, the sum is reported. [c] Process temperature and time for completion of the intended Diels–Alder reaction. [d] Calculated from AKTS modeling based on dynamic DSC of the final reaction mixture with different heating rates. T_{D24} = 162 °C for **2c**.

Dienophile **2a** was used to prepare the first kg batches of **4** as initial Diels–Alder reactions with **2b** and **2c** led to excessive polymerization. Later, we found that TEMPO stabilized the Diels–Alder reaction of **2b** with **1** (*17*). Luckily, TEMPO did prove effective as well with **2c**. TEMPO was therefore added to all Diels–Alder reactions with **2b** and **2c**.

For the neat reactions, the DSC traces gave a good picture of the desired reaction in the absence of solvent (*11*). The traces displayed two major exothermic events. The first event started at low temperatures (68–72 °C) and was attributed to the desired Diels-Alder reaction. The energy correlated well with the energy measured by reaction calorimetry (approximately –300 kJ/kg for reactions with **2a** and **2b**). The second exothermic event occured at higher temperatures (250–400 °C) and is attributed to decomposition of the Diels–Alder product. In the DSC of **2a** and **2b** with **1**, the two exothermic events of the desired reaction and the decomposition reaction are even overlapping, which is a severe safety concern. For **2c**, the two exothermic events are separated and reported separately. The peak temperature of this first exotherm of the reactions of **2a**, **2b**, and **2c** with **1** is decreasing which is in line with the trend of the process temperatures T_p of the neat Diels–Alder reactions: the reactivity is increasing in the order **2a**, **2b**, **2c**.

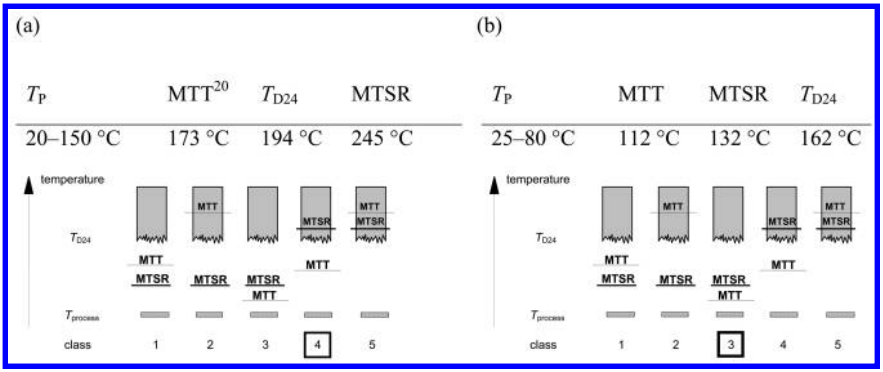
While the value of T_p for **2c** is given for the reaction in toluene, the reaction also runs at 65 °C without solvent albeit slower. The exothermic potential is high for all three reactions. Prolonged exposure at higher temperature should be minimized as the secondary reactions (decompositions) bear both the risk of runaways and a quality risk by producing tarry byproducts. The goal is to mitigate the thermal risk which might be achieved by dilution. This not only would reduce the energy accordingly but would establish an upper limit to heating due to the boiling point of the solvent and increase of the heat capacity.

The Diels–Alder reactions of **2a** and **2c** were studied by heat flow reaction calorimetry at 300-g scale (RC1) (*11*). Both neat reactions gave similar results: the heat of reaction was approximately –300 kJ/kg, and the MTSR equaled approximately 250 °C (Table 2) (*18*). At this temperature, the decomposition would be too rapid, leading to final reaction temperatures of >400 °C. On the other hand, the reactions using **2a** took several days when it was run in solvents, while using **2c** showed a decent reaction time at 100 °C in toluene. RC1 data for the diluted Diels–Alder reaction of **2c** with **1** resulted in a much decreased MTSR of 132 °C.

Lastly, the probability of a runaway had to be assessed. To this end, the stability of the final reaction mixtures was studied by recording dynamic DSC measurements with different heating rates. Thermokinetic modeling according to the 'isoconversional' method (AKTS-Thermokinetics Software, Version 3.22) afforded the TMR_{ad} at the MTSR. For **2a**, the runaway would take 40 min at 245 °C, whereas for **2c**, the exothermic decomposition would take > 800 h at the MTSR of 132 °C. In conclusion, chloroacrylonitrile **2c** showed clear superiority over **2a** and **2b** based on these safety data.

A systematic safety assessment is ideally carried out with a Stoessel criticality diagram (*19*), arranging the critical temperatures T_p (process temperature), MTT (maximum technical temperature, here: bp), T_{D24} (temperature at which TMR_{ad} = 24 h), and MTSR (maximum temperature of the synthesis reaction) in increasing order (Figure 3). Depending on the order of these temperatures, five different types of scenarios are defined. These criticality classes are helpful for assessing the risk and to propose measures how to control the risk. In criticality class 2, for example, after loss of control of the desired reaction, the technical limit cannot be reached as MTSR < MTT. MTSR is below T_{D24}, i.e. the below the highest temperature at which the thermal stability of the reaction mass is unproblematic. Therefore, the decomposition reaction (visualized by the grey zone above T_{D24}) cannot be triggered. For the reaction of **1** with the dienophiles **2a** and **2c**, the criticality classes **4** and **3** were allocated, respectively. In class 3, loss of control of the synthesis reaction will lead to boiling of the mixture (MTT) but the decomposition cannot be triggered (MTSR < T_{D24}). In class 4, after reaching the bp due to loss of control of the synthesis reaction, the decomposition reaction could potentially be triggered (MTSR > T_{D24}). In both cases, reaching the bp could be a hazard if the heat release rate at MTT cannot be compensated by the heat removal rate. Class 4 is more critical than class 3 as decomposition reactions will be triggered if the technical measures (like evaporative cooling) fail.

Based on these safety analyses, chloroacrylonitrile **2c** is preferred over the other dieneophiles and was chosen for the manufacturing of >400 kg of **3**.



(a)

T_P	MTT[20]	T_{D24}	MTSR
20–150 °C	173 °C	194 °C	245 °C

(b)

T_P	MTT	MTSR	T_{D24}
25–80 °C	112 °C	132 °C	162 °C

Figure 3. Characteristic temperatures for the batch reaction of (a) ***1*** *with* ***2a*** *(neat), and (b) with* ***2c*** *(34% in toluene), arranged in increasing order, and represented in the Stoessel criticality diagrams.*

According to the definition of the criticality class 3, the safety of this process is dependent on the heat release rate of the synthesis reaction at the boiling point. In other words, the design of the reactor must accommodate unhindered evaporation and condensation of volatiles. The corresponding three major risks are described in the following paragraphs. A more detailed discussion, including the underlying calculations, was described elsewhere (*11*).

First, the so called boiling barrier as a safety measure relies on the availability of enough toluene to absorb the excess energy in case of a runaway. The required amount of solvent can be estimated from the heat release rate derived from the DSC of the starting materials at the boiling point of toluene, the reaction energy, and the evaporation enthalpy of toluene. With a dilution of 34% w/w there will be always enough toluene available to maintain a safe profile.

Second, the condenser surface must be large enough to absorb the maximum amount of heat that evaporation will bring to the condenser. The typical condenser heat exchange area used in the plant is much larger than the minimally required 0.12 m^2.

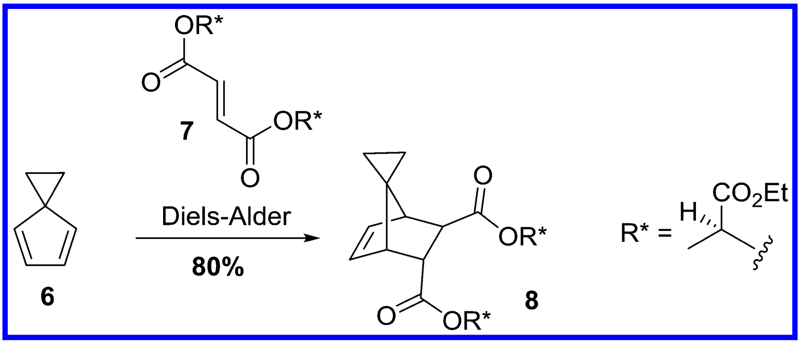
Third, the vapor streams must be able to flow through the exhaust pipe (vent line) in an unhindered way without overpressure formation. As a rule of thumb, the velocity of the vapors should not exceed 10 m/s. In the present case, even a very small diameter of 0.03 m would be compatible with this requirement. This study was performed for a batch size of 100 kg.

The above safety assessments, that were run in parallel to initial route finding activities, homed in on the choice of chloroacrylonitrile **2c** for the safe scale-up of the diluted Diels–Alder reaction with diene **1** to ultimately deliver more than 400 kg of bicycle **3**. In practice, a mixture of the Diels–Alder reagents **1** and **2c**, $NaHCO_3$, and TEMPO in toluene was heated to 100 °C for 15–20 h to produce the bicycle **3**. The MTSR for the adiabatic worst case situation at the end of the heat ramp would be 132 °C. The boiling barrier of toluene sets in at 112 °C. The adaption of this hazardous reaction to a safe scale-up enabled the expeditious production of the API **5** for imminent clinical studies. As this "fit-for-purpose" route suffered from the scale limitation imposed by the safety assessment (no higher than approximately 100-kg batch size) (*21*), alternative routes were ultimatively developed to pave the way for larger quantities of the chiral bicyclic ketone **4** (*22*, *23*).

Process Development and Hazard Analysis of Spiro[2,4]hepta-4,6-diene (6)

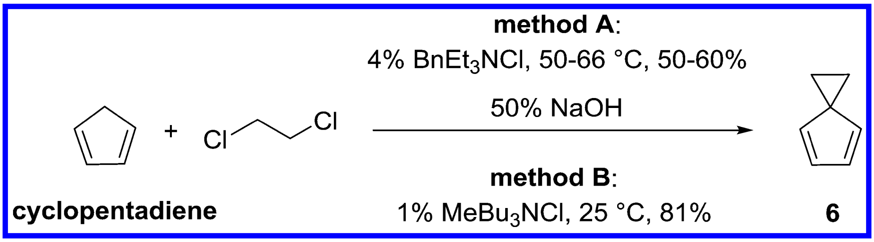
Development of a Scalable Synthesis of Spiro[2,4]hepta-4,6-diene (6)

Spiro[2,4]hepta-4,6-diene (**6**) was reacted with di-(1*S*)-1-ethoxycarbonylethyl fumarate in methylcyclohexane to effect the Diels–Alder reaction at room temperature for 20 h (Scheme 2) (*24*).



*Scheme 2. Diene **6** used for the Diels–Alder reaction with a chiral fumarate ester 7 (25) for the production of enantiomerically pure tricyclic intermediate **8**.*

Several syntheses of the diene **6** are reported. They can be classified as reactions either with (*26–29*) or without (*30–33*) a phase-transfer catalyst (PTC). The first amounts of cyclopropylcyclopentadiene (**6**) were produced via geminal dialkylation of freshly distilled cyclopentadiene with 1,2-dichloroethane under phase transfer catalysis conditions in aqueous NaOH following the protocol by Coe et al. (*29*) (Scheme 3). Cyclopentadiene should not be stored due to its highly exothermic dimerization even at low temperatures (*34*, *35*). Therefore, it was always freshly prepared by batch distillation ("cracking" of dicyclopentadiene (*36*)) on a limited scale (300 g) (*37*). Freshly prepared cyclopentadiene was used immediately to minimize hazards. In the DSC trace of cyclopentadiene, a total of –890 kJ/kg energy is released starting at 60 °C.



Scheme 3. Synthesis of **6** *from cyclopentadiene under PTC conditions (yields are presented for distilled* **6***)*

The germinal dialkylation was conducted according to the published protocol (*29*): a mixture of freshly prepared cyclopentadiene and 1,2-dichloroethane was added to a mixture of 50% aq NaOH and benzyltriethylammonium chloride at 50–66 °C (method A in Scheme 3). The two reaction partners were continuously charged to the base solution over 1–1.5 h. After a simple aqueous wash, the crude oil was obtained in ~ 90% yield. However, the quality of the product was not sufficient for the next step. ^{1}H NMR spectroscopy showed unidentified byproducts while GC–MS indicated only an area purity of approximately 90%. After purification by distillation, **6** was obtained in 50–60% yield without byproducts. For product analysis during the following optimization, ^{1}H NMR spectroscopy was used. Several batches were produced on 100-g scale as a precursor for improving the process for further scale-up.

The low onset temperature of the exothermic decomposition of **6** (80 °C) in the DSC experiments (Figure 4) and the boiling point of cyclopentadiene (39–43 °C) called for a lower reaction temperature. Further goals have been to increase the yield, to reduce catalyst loading, and possibly augment the purity of the product so that the distillation of the product could be skipped. Moreover, we did not want to pre-mix cyclopentadiene and 1,2-dichloroethane in a separate vessel due to the inherent instability of cyclopentadiene, but rather distill it directly into a vessel containing the base so as to prepare the solution of the cyclopentadiene sodium salt.

As a model for our reaction, researchers at DSM had used ~5 mol% of Aliquat 336 (*38*) as catalyst for the synthesis of tri- and tetra-alkylated cyclopentadiene with alkyl halogenides (*39*). When employing this catalyst, the reaction took place readily at only 25 °C, a temperature that would not lead to the exothermic decomposition of the substrates (*40*). In a modified order of addition, cyclopentadiene was added to a mixture of 50% NaOH and 0.5 mol% of Aliquat 336 at 25 °C producing the typical red color of the cyclopentadiene anion (pK_a 15). 1,2-Dichloroethane (1.0 equiv) was then dosed to the solution over 1 h with cooling (*41*). The mixture was further stirred for 3 h and following work-up, the crude product was obtained in ~80% yield. This route produced a much higher purity (**6**: dichloroethane ~ 98:2 as compared to ~ 66:34 for method A). Distillation afforded **6** in a yield of 70%. Although Aliquat 336 was a very efficient catalyst, it was deleterious for the workup. The phase separations became problematic and some catalyst remained in the organic phase. Even more troublesome was that this impurity was impeding a critical crystallization at a later stage. Therefore, purification by distillation was mandatory for the Aliquat process. Instead, we sought an efficient but less lipophilic PTC to mitigate the workup problems. To our delight, methyltributylammonium chloride was as efficient as Aliquat 336 without causing the existing problems during the aqueous workup. Using 0.7–1 mol% of catalyst reduced the reaction time to below 2 h if 1,2-dichloroethane was dosed over 1–2 h. (method B in Scheme 3). Once ^{1}H NMR indicated a complete conversion, the reaction mixture was worked up by a simple aqueous extraction. Method B produced 98% yield of the diene **6** and the ^{1}H NMR indicated a clean spectrum without byproducts. Distillation of the product afforded **6** as a colorless liquid in 81% yield (*42*). However, to our satisfaction, crude **6** obtained by method B was pure enough to give similar results in the Diels–Alder reaction as the distilled material and thus the distillation was no longer required.

Reaction calorimetry was performed to design a process with only minor reagent accumulation at room temperature and to determine the maximum heat flow. Such experiments are required to ascertain if the reactor cooling capacity is large enough to avoid a dangerous temperature rise. To this end, 1,2-dichloroethane was added over 15 and 60 min to a mixture of cyclopentadiene in 50% NaOH and Aliquat 336 (Table 3). The first experiment displayed 75% accumulation by the end of addition, an unacceptable situation. By prolonging the addition time in the second experiment by a factor of four, the accumulation decreased to 5%. Both experiments displayed a high maximum heat release rate (80–100 W/kg). To reduce this heat flow, 1,2-dichloroethane should be dosed over greater than 1 h and dilution would further reduce the maximum heat flow. For glass-lined steel reactors at pilot plant scale, values of 40–50 W/kg are ideal for maximum reaction rate coupled with a safe level of heat removal. Steel reactors are preferred as they possess a high heat transfer coefficient allowing for efficient cooling.

The diene **6** was stable for at least three weeks at –20 °C and at 18 °C for at least two weeks. Cyclopentadiene and **6** have a pungent smell. For decontamination of small spillages and for pre-treatment of glassware prior cleaning, it proved efficient to use a solution of maleic anhydride in DMF to render the diene unreactive and safe for disposal.

Assessment of the Thermal Stability of Spiro[2,4]hepta-4,6-diene (6)

The first laboratory scale syntheses of **6** (method A) were carried out at 50–60 °C, very close to the onset temperature of cyclopentadiene and **6** (60 and 80 °C, respectively), and diene **6** was distilled at 60 °C jacket temperature and 35 mbar (bp of **6**: 30-32 °C). Hence, the reaction and the distillation were judged as being untenable for a safe process. A batch distillation on larger scale will inevitably lead to prolonged thermal stress due to the unavoidable extended heating period. Even though our improved protocol (method B) did not require a distillation, such a purification might be necessary for some batches of **6** in the future. Therefore, the following safety assessments were performed to identify a safe distillation temperature for **6**.

(1) Dynamic DSC measurements of three different samples: crude undistilled **6**, distilled product **6**, and the distillation residue.
(2) thermokinetic modeling of the decomposition reaction.
(3) Dynamic C80 experiments (see Abbreviations) should deliver the pressure increase.

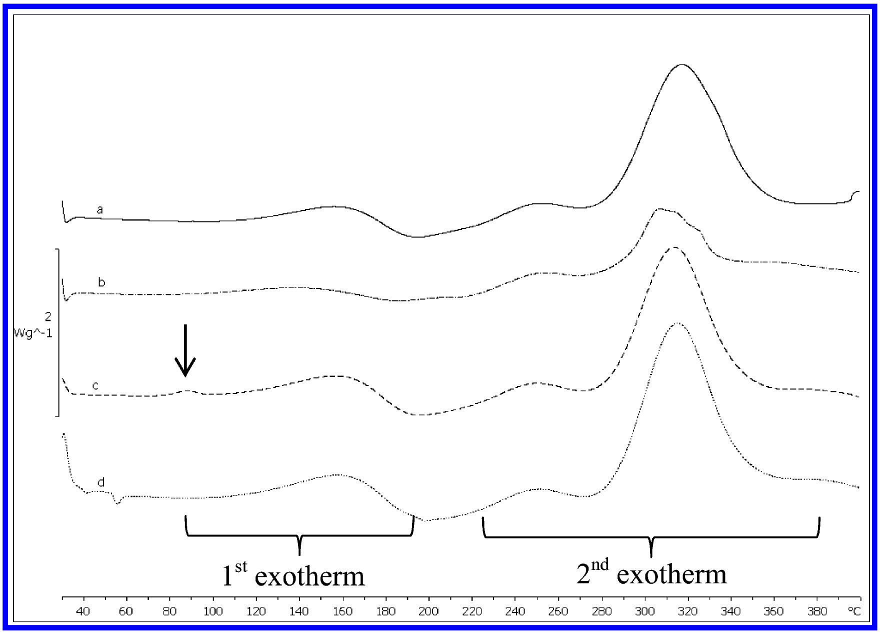


*Figure 4. DSC traces of (a) crude **6** under argon, (b) distillation residue after distilling **6** under argon, (c) distilled **6** under air, and (d) distilled **6** under argon. The arrow on curve (c) indicates the additional exothermic event observed under air.*

Table 3. Reaction calorimetry data for the alkylation of cyclopentadiene with 1,2-dichloroethane dosage over (a) 15 min, and (b) 60 min[a]

exp.	*reaction heat Q_R (kJ/kg)*	*reaction enthalpy ΔH_R (kJ/mol)*	*maximum heat release (W/kg)*	*thermal conv. at the end of addition (%)*
(a)	–235	–220	100	25
(b)	–211	–209	80	95

[a] Cyclopentadiene (13.2 g) with 1,2-dichloroethane (1 equiv) and Aliquat 336 (0.1 equiv) in 50% NaOH at 25 °C, 250–300 rpm (Systag Flexicube reactor, Flexisys software).

Thermal Screening of the Samples under Air or Argon Atmosphere

Due to the anticipated propensity of electron-rich **6** toward oxidation, all three samples were screened by DSC under both air and argon atmospheres (Figure 4 and Table 4). Two main exothermic events can be distinguished in the profile of the dynamic measurements. The first exotherm starts at a low temperature, close to the jacket temperature (50 °C) of the distillation vessel. The second exotherm beginning at ~220 °C was very large with a high potential for all samples, i.e. > 1000 kJ/kg. However, it is evident from the measurements that contact with air introduces a thermal activity at lower temperatures (in the range 66–95 °C, < –50 kJ/kg) rendering the air exposed samples inherently more hazardous (compare Figure 4c with 4d). Hence, it is recommended to avoid contact with oxygen to improve the thermal stability of the mixtures. Consequently, for simplicity the following assessment considers the thermal stabilities under the inert atmosphere only.

Table 4. DSC data extracted from curves (a)–(d) as illustrated in Figure 4. [a]

	*crude **6** under argon*	*distillation residue after distilling **6**, under argon*	*distilled **6**, under air*	*distilled **6**, under argon*
	(a)	(b)	(c)	(d)
1st exotherm				
from	94 °C	75 °C	66 °C	84 °C
to	177 °C	168 °C	180 °C	182 °C
T_{peak}	156 °C	137 °C	157 °C	158 °C
Q_R (kJ/kg)	–109	–62	–211	–219
2nd exotherm				
from	226 °C	211 °C	223 °C	226 °C
to	381 °C	> 400 °C	> 400 °C	> 400 °C
T_{peak}	317 °C	307 °C	314 °C	315 °C
Q_R (kJ/kg)	–1215	> –1074	> –1376	> –1799

[a] The endotherm between the two exothermic events is not reported.

Thermal Stability of Crude 6 and of the Distillation Residue

The DSC experiments of crude **6** and of the distillation residue (Figure 4a and 4b and Table 4) show a first smaller and a second larger exothermic event with high severity. Extrapolating to plant scale, the first exothermic events would cause self-heating at the intended process temperature of 50 °C. Under ideal adiabatic conditions, this exothermic event would raise the temperature of crude **6** and of the distillation residue by either 64 and 37 K, respectively. When starting from 50 °C, the maximum temperature would be either 114 and 87 °C, respectively, which is close to the anticipated boiling point of **6** under normal pressure (128

°C) (*43*). At these temperatures, the second very large exotherm would not be in reach to cause self-heating particularly when assuming conservative natural heat losses. Additionally, in the intended open system, non-hazardous evaporative cooling would prevent reaching or surpassing the maximum attainable temperature of 114 °C. Consequently, both the crude **6** and the distillation residue would not lead to hazardous self-heating at the proposed vacuum distillation temperature at a maximum jacket temperature of 50 °C.

Thermal Stability of Distilled 6

The thermal stability of distilled **6** was screened by DSC (Figure 4c and 4d, Table 4) and the Calvet calorimeter C80 (Figure 6). These three measurements show a large leading exotherm of medium severity starting at a low temperature followed by an endotherm that directly leads into a very large exotherm over –1300 kJ/kg starting at 192–226 °C. It follows that the first exotherm would potentially cause self-heating from the intended process temperature of 50 °C up to 190 °C which would trigger the second very large exotherm, with the potential to reach temperatures above 1000 °C.

Of all the samples, the purified **6** showed the largest decomposition energy. Therefore, purified **6** was chosen for the isothermal DSC measurements at 100, 110, 120, and 130 °C to shed light on the probability of runaways by determining the TMR_{ad} at various temperatures (Table 5).

Table 5. Results of the isothermal DSC measurement (24 h) with distilled 6.

entry	*temperature (°C)*	*maximum heat release rate at peak (mW/kg)*	t_{peak} *(min)*
1	100	27.81	2.24
2	110	63.77	2.24
3	120	90.87	2.20
4	130	170.04	2.10

The thermogram profiles lead to the conclusion that the decomposition kinetics of the first peak is of normal nth order (Figure 5). The logarithm of the maximum heat release rate was plotted against 1/T (Arrhenius) which allowed to determine the activation energy of this decomposition (72 kJ/mol) with a reference heat generation rate of 55 W/kg at 110 °C (*19*). Based on this data, the TMR_{ad} for the first exotherm was estimated to be 6.9 h at the intended process temperature (maximum jacket temperature) of 50 °C. Hence, the thermal risk of this decomposition should be regarded as high. Typically, a TMR_{ad} of > 24 h is considered as low risk, allowing time for improvised safety measures. For this first exothermic event, the TMR_{ad} is 24 h if run at approximately 35 °C.

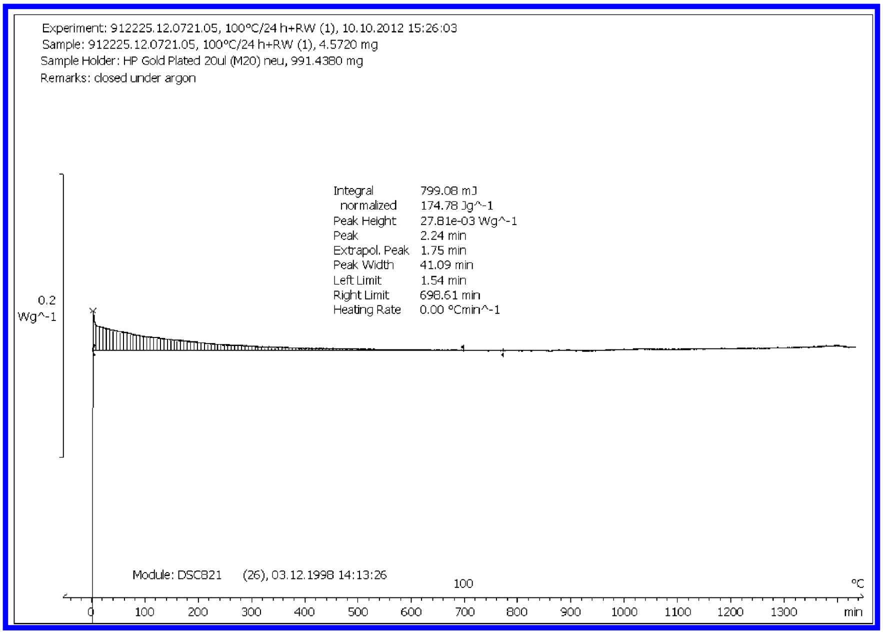


*Figure 5. Isothermal DSC of distilled **6** at 100 °C for 24 h. Maximum heat release rate = 27.81 mW/g, t_{peak} = 2.24 min.*

The residual heat profiles of the DSC samples *after* the isothermal measurements indicate the same heat for all four samples (approximately –1350 kJ/kg). As an example, Figure 6 shows the DSC that was measured of a sample after exposure to 100 °C for 24 h. Apparently, during this period, the second large exotherm was not yet triggered. The profile of the thermograms suggests an autocatalytic decomposition behavior of this large second peak which makes the decomposition kinetics potentially sensitive to contaminations that might catalyze the decomposition.

The C80 measurement (Figure 7) did not show any production of non-condensable gas, thus any pressure build-up due to gaseous decomposition products was not considered in this assessment.

Distilled **6** will only be found in the distillation vessel as vapor or as a thin liquid film on the vessel surfaces. If distilled material could accumulate in the distillation vessel (e.g. in low areas of piping) the temperature of distilled **6** is limited to the boiling temperature, which is assumed to be below 128 °C at normal pressure. At 128 °C, non-hazardous evaporative cooling would compensate for the generated heat of decomposition, i.e. will act as a cooling barrier. The heat generation due to the very large second exotherm is small at this temperature. Hence, the hazard of distilled **6** in the vessel is insignificant.

In conclusion, distilled **6**–despite its high thermal risk–would not cause hazardous self-heating at the proposed maximum process temperature of 50 °C, provided it will be handled in an open system under inert atmosphere.

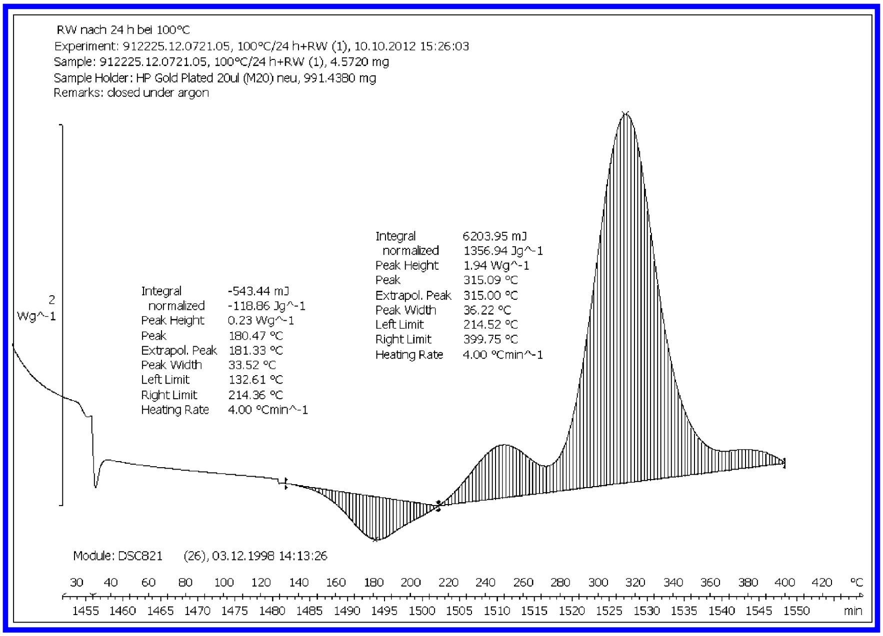


*Figure 6. DSC measured after heating **6** at 100 °C for 24 h. Residual heat = –1357 J/g.*

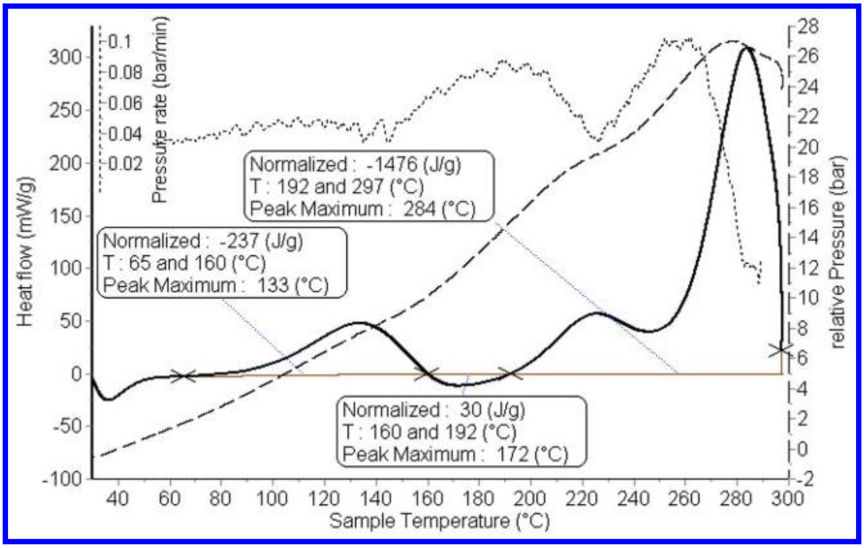


*Figure 7. C80 experiment with distilled **6**, under argon, heating rate 0.5 °C / min, from 30–300 °C. Line code: dotted line (pressure rate), dashed (pressure), solid (heat flow).*

Conclusions for Spiro[2,4]hepta-4,6-diene 6 Safety Analysis

The conclusions achieved for **6** in this safety analysis are limited for the intended scale of 10 kg. This was due to the overall large thermal potential of the samples and the difficulty to anticipate sensitivity towards contaminants (for example metals, acids, bases), which may accelerate the second exotherm of high severity significantly. While we feel confident in our safety examination and conclusions, it is best to err on the side of caution and limit the batch size at this stage of development. The most appropriate basis of safety for the distillation of crude spiro[2,4]hepta-4,6-diene (**6**) is process control. This is achieved by implementing the following precautions:

- Compound **6** should only be handled and kept under inert atmosphere.
- Compound **6** should be kept free from contaminations to avoid catalysing potential decomposition reactions.
- The distillation should be carried at the intended jacket temperature of 50 °C.
- The residence time of **6** in the head space should be kept as short as practically possible. This could be achieved by the application of reduced pressure and/or a nitrogen trickle flow through the distillation vessel to move distillate to the receiving vessel quickly.
- Storage of **6** at 25 °C under inert atmosphere should be limited to individual units of less than 13 L (~10 kg); this is based on the above data and some additional conservative assumptions using the thermal explosion model (*44*). Due to the thermal potential of **6**, a milder distillation method (e.g. thin layer or wiped film evaporation) should be considered for further scale-up.

Continuous Flow Technology for Hazardous Reactions

The use of flow reactors allows to control hazards, especially of exothermic full-batch reactions like the Diels–Alder reaction of acrylonitriles **2** with diene **1**. The solvent-free reaction of acrylonitrile **2a** with **1** was transferred into a simple flow reactor consisting of a coiled steel tube, running at 215 °C with residence times of approximately 1 min (*45*). The crude yield being comparable to the batch reaction, this application served as contingency should the batch mode prove to be unsuitable for scale-up.

The exothermic dialkylation of cyclopentadiene to cyclopropyl-cyclopentadiene **6** runs at a temperature close to the onset temperatures of both cyclopentadiene and the bicycle **6**. A flow reactor was developed that minimized the volume of reaction mixture exposed to the process temperature of 40 °C as compared to the batch process described above. This increased the inherent safety of this reaction with a highly energetic starting material and product (*46*).

Conclusions

Two examples of hazardous reactions have been presented to demonstrate the benefit of fully exploring the thermal risk assessment early in development. For the scale-up of the Diels–Alder reaction with cyclohexa-1,5-dien-1-yloxy)trimethylsilane (**1**) to pilot plant scale, chloroacrylonitrile (**2c**) was chosen amongst three dienophiles based on a thorough safety assessment in conjunction with other factors such as the number of overall steps, availability of raw materials, and ultimatively the need to deliver material quickly and safely! The safety assessment sets a limit for the mass of the Diels–Alder reaction of **2c** with **1** at approximately 10-kg scale. The second example, spiro[2,4]hepta-4,6-diene (**6**) is a highly reactive diene with a large thermal potential. Both the highly exothermic synthesis and the subsequent purification by distillation required an adequate thermal assessment. DSC, C80, and reaction calorimetric experiments provided the basis for a sound and data-based assessment of the risks for the intended scale, resulting in the rapid delivery of kilogram quantities of these intermediates to meet urgent clinical milestones. In a broader perspective, an early risk assessment has the strong potential to reduce the gap between the selection of a clinical candidate and the first clinical trials, and ultimately paves the way to a more expeditious delivery of life-saving medications to patients.

Acknowledgments

We thank Daniel Marchal for the reaction calorimetric experiments. Dr. Thomas Weller is warmly thanked for continuous support. Arran (Ireland) is acknowledged for manufacturing of **2c**.

Abbreviations

C80: Differential calorimeter of the Calvet type (commercially available from Setaram) with a high sensitivity thanks to its 3D sensor sytem (about 10–100 times more sensitive than DSC), which can be used with a high pressure cell allowing for pressure measurement.

DSC: Differential Scanning Calorimetry

100-K rule: rule of thumb saying that 100 K below the DSC onset temperature there will be “no risk” of hazardous self-heating.

MTSR: maximum temperature of the synthesis reaction

MTT: maximum technical temperature, here: bp.

Onset temperature: in the context of thermal process safety, the onset temperature is the temperature where the equipment first detects the heat generation of the peak, i.e. left temperature limit of the peak. This should not be confused with the “onset temperature” reported in most scanning calorimeters which is used for the determination of phase transfers, e.g. melts.

RC1: bench scale heat flow calorimeter from Mettler-Toledo.

TMR_{ad}: time to reach the maximum rate of decomposition due to self-heating of the material under adiabatic conditions.

ΔT_{ad}: adiabatic temperature raise

T_{D24}: temperature at which TMR_{ad} = 24 h. It is the highest temperature at which the thermal stability of the reaction mass is unproblematic.

Tp: process temperature

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Chapter 8

Rapid Scale Up Using Hazardous Reagents: The Challenge of Risk Mitigation

Noel A. Hamill*,[1] and Mark E. Howells[2]

[1]Almac Sciences, Seagoe Industrial Estate, Craigavon, UK, BT63 5QD
[2]Novozymes A/S, Hallas Allé 1, 4400 Kalundborg, Denmark
***E-mail: noel.hamill@almacgroup.com**

The safe management of hazardous reagents is a key part of the transition from medicinal chemistry syntheses to pilot scale processes. The detection, investigation and circumvention of the risks associated with their use at scale are elucidated through six case studies from the contract manufacturing sector. An approach for the successful scale up using hazardous reagents is described, involving the combination of chemical hazard assessment and 'holistic process design', where the integration of hazard reduction measures and the maintenance of product quality should be viewed with equal importance.

Introduction

A hazardous reagent is a substance that could potentially cause harm to life and health, damage property or harm the environment. Given their ubiquity in modern preparative methods, safe handling of these reagents is a routine feature of synthesis for an experienced organic chemist. Beyond the obvious challenge of larger quantities, why should safe handling be any different at scale (i.e. in large scale plant equipment)?

Before addressing hazardous reagents at scale, it is necessary to consider why reactions become more hazardous as scale increases. The principal hazards associated with chemical reactions are exothermicity (heat evolution) and loss of containment (gas evolution or vapour due to the heat evolution) (*1*). Both of these hazards require adequate surface area to maintain control; jacket services for cooling the walls and a liquid/headspace interface for gas disengagement respectively. Unfortunately, as reactors increase in size, the ratio of surface area to volume decreases dramatically, and as a result the risk of scaling up a seemingly innocuous lab reaction increases with respect to heat removal and the danger of pressure from gas evolution. To compound this problem, reaction rate and thus heat evolution for exothermic reactions increases exponentially with temperature, whereas the cooling rate is linear with increasing temperature, leading to the risk of an uncontrolled 'runaway' scenario, as shown in Figure 1.

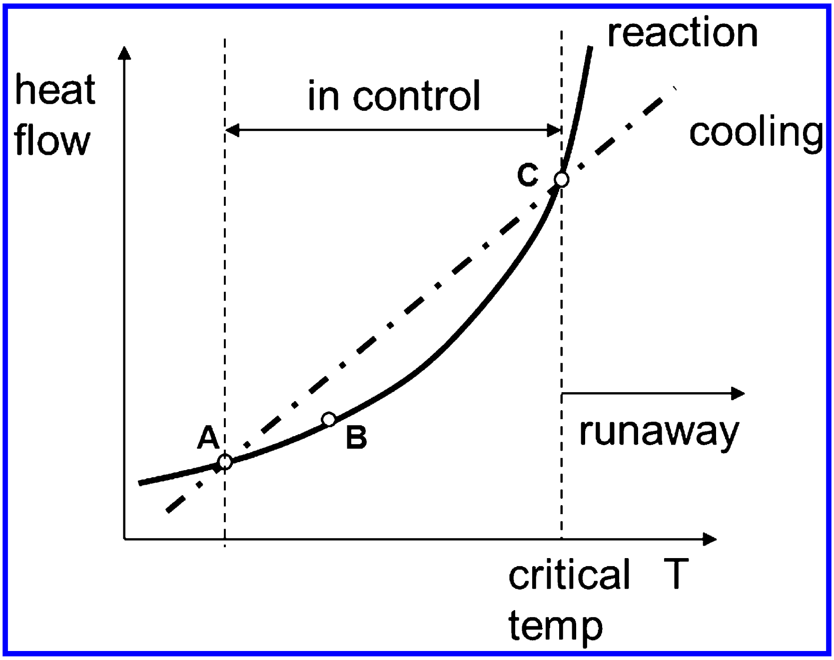

Figure 1. Heat flow in reactors as a function of temperature (Semenov diagram)

In order to prevent incidents at larger scale, hazardous reactions are investigated using a) adiabatic calorimetry, in which the effects of the 'undesired' runaway reactions can be assessed in a lab scale vessel (~10 mL) by simulating heat loss experienced at large scale, and b) reaction calorimetry, in which the rates of heat and gas evolution of the 'desired' reaction are measured.

A detailed exploration of calorimetry and data interpretation is beyond the scope of this chapter (see refs (*2*) & (*3*)). Although there are many commercial systems available, the main instrument referred to in this chapter is an adiabatic calorimeter known as the Advanced Reactive System Screening Tool (ARSST, Fauske Inc., Figure 2).

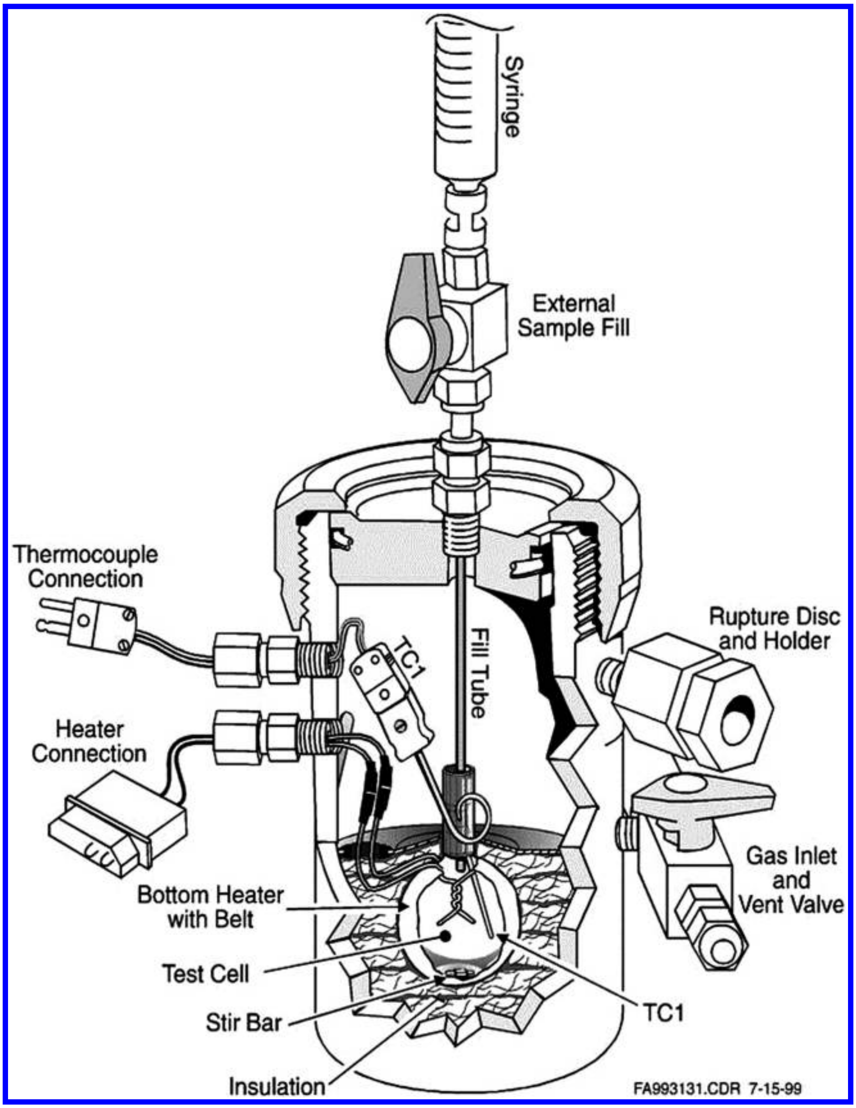

Figure 2. Schematic of the Advanced Reaction System Screening Tool (ARSST). (Reproduced with permission from reference (4). Copyright (1999) Fauske and Associates, LLC)

This system simulates the adiabatic conditions in large scale vessels by heating an aliquot of reaction mixture (~10 mL) contained within a well insulated, unsealed, thin walled glass cell. As in large scale vessels, the vessel mass tends to be a small proportion of the overall mass and almost all of the exothermicity is absorbed by the vessel contents, further accelerating the reaction. An inert pressure pad of nitrogen gas (typically 1-20 bar) is also employed to prevent tempering of the exotherm by vaporization of solvent. The self-heating rate and pressure rise associated with gas evolution can therefore be monitored as a function of temperature.

The data analysis of the calorimetry experiments can be fairly sophisticated but three important concepts commonly encountered are:

- adiabatic temperature rise (ATR)
- temperature of no return (TNR)
- time to maximum rate (TMR).

The ATR is the increase in temperature which would result if no heat were removed from the system. As the heat of the desired reaction may precipitate unforeseen decomposition reactions, this number can be higher than expected. Typically, values over 50 °C would raise concerns for scale up and require careful investigation. The TNR is point C in Figure 1, where the reaction is no longer in control. This will be equipment dependent and therefore must be recalculated on changing scale or vessel. TMR is a useful parameter as it signifies the amount of time available to personnel to rectify an adverse event (e.g. loss of cooling or agitation) before the worst effects are realized. Although obviously dependent on levels of plant supervision, running a process with a TMR of less than 8 h would be regarded as risky. A more thorough discourse on these concepts can be found in ref (*3*).

In an ideal world, an exhaustive investigation of all reaction steps would be performed before scale up. However, in early phase development and particularly in the contract manufacturing sector, there are a number of factors which impact hazard assessment:

- **Tight timelines**. Client deadlines for producing the first few kilograms of material are usually very tight. Thus the development and scale up of a six step medicinal chemistry synthesis route within 3-4 months is a common occurrence.
- **Long lead time of raw materials**. Typically, the scalable route will have to be developed using general purpose reagents due to the long lead times involved in the delivery of the bulk supplies. The bulk reagents may have different impurity profiles which can affect the reactivity of the reaction mixture and thus the safety of the chemical step. The time available to resolve any such difficulties late into development is usually limited.
- **Limited budget**. Although adequate resources are available to permit safe scale up, the budget will rarely permit all of the potentially hazardous scenarios to be fully investigated. A risk assessment is performed in order to prioritize resources; this will lead to safe operating conditions

but perhaps with less than optimal results (longer reaction times, lower yields, higher costs, etc.)

- **Varied chemistry**. Implementing new syntheses means that some reagents may never have had a thermal hazard assessment conducted on them before.
- **Not invented here**. Where chemical development has taken place elsewhere, there is only a brief period for process familiarization and the hazardous factors may not be adequately communicated during technology transfer. Poor transfer of information may result in hazardous scenarios (unrealized errors in mixing reagents, order of addition is important, etc.)
- **Unproven at >100g scale**. Off-gassing and exotherms can easily be missed in small lab scale vessels where these phenomena are difficult to detect. Many reactions are mistakenly labelled as ‘safe’ because they have been performed dozens of times at lab scale without incident.

Even with all of these limitations in place, there is a duty of care for manufacturers to protect their staff, property and environment.

In practice, the usual approach is to risk assess the chemical synthesis at the outset by recognizing ‘trigger groups,’ such as nitro- or peroxy- moieties and consult the available literature resources for precedence of adverse events associated with the reagents. Foremost of these resources for hazardous reagents is Bretherick’s Handbook of Reactive Chemical Hazards (*5*) and the Journal of Loss Prevention in the Process Industries (*6*). The internet and literature databases are also readily accessible sources of information which should be exploited.

In guiding the safety evaluation, the hierarchy of hazard control (*7*) is an important tool. A widely used concept in manufacturing, it states that the preferred order of dealing with hazards is in the following order: elimination, substitution, engineering control, procedural control and finally personal protection equipment. With respect to hazardous reagents, process chemists will often seek to eliminate or substitute them with less hazardous alternatives. However, due to the pressures outlined above, finding alternative reagents or intermediates may not be feasible and thus it is often engineering and process control measures which ultimately allow the process to be run safely.

It is widely accepted that as part of the transfer of the process from the development team to manufacturing, a hazards review meeting should take place. Within our organization, and indeed across the chemical industry, the most widespread example is the hazard and operability study (HAZOP). This approach, or a similar variant, aims to identify risks in a systematic way by using guided prompts, such as ‘what happens if we charge…too much of X, too little of X, in the wrong order, Y instead of …etc’. In this way, hazard and operability issues are identified, ranked and impact assessed. Appreciation of the probability and the severity of the risk then defines the measures put in place to mitigate the risk.

Even in following a conscientious best practice approach to hazard assessment as described above, there are some scenarios which occur frequently and are elucidated in this chapter from our case studies. These will serve to provide examples to the conscientious process scientist to avoid similar dangers in their work. While we recognize that hazardous chemistry also includes toxicity, corrosivity, and sensitization to chemicals, our chapter will deal exclusively with the hazards of thermal events.

Sometimes Impurities, Not Reactants, Are the Cause of Hazardous Conditions

A review of the desired chemistry and possible side reactions is a key step in the hazard assessment process. In most cases, the chemists and engineers will only have the knowledge of the reagents at their disposal. The impurity profile of the intermediates and reagents may be unknown and indeed, may vary from batch to batch. How is it possible to consider all possible adverse scenarios in a timely manner? Fortunately, a small subset of chemical entities is responsible for the majority of undesired events relating to impurities. One should consider the impact of the following materials on each processing step during the initial literature search / hazard assessment, i.e. at the same time as identifying trigger groups and exotherms in the desired reaction.

- **Metals** – for example, trace amounts of catalysts (Pd, Pt, Fe, etc.) or exposure to materials of construction (steel, brass, nickel alloys etc.).
- **Acids and bases** – catalyze many organic reactions, may remain in overhead equipment or enter vessels accidentally from scrubbers / vent lines during operation.
- **Water** – may hydrolyze reagents during supposedly 'anhydrous' reactions, initiating acid and base catalyzed chemistry. Residual water may remain from cleaning transfer lines, overhead equipment and vessels, or from ingress of humid air.
- **Peroxides** – may initiate free radical reactions. The main sources are oxygen (from air) and ethereal solvents, especially THF.

m-Chloroperoxybenzoic Acid (*m*CPBA)

The peroxyacids are powerful oxidants among which substituted aromatic peroxyacids, such as *m*-chloroperoxybenzoic acid (*m*CPBA) (Figure 3), are sufficiently stable to allow general use in scalable organic synthesis. *m*CPBA is most commonly employed for use in the epoxidation of alkenes, the transformation of ketones into esters (i.e. the Bayer-Villiger reaction), and the selective oxidation of thioethers to sulfones/sulfoxides and amines to *N*-oxides/nitro groups (*8*).

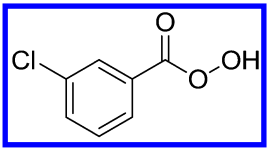

*Figure 3. Chemical structure of m*CPBA

An adverse event specific to *m*CPBA was known from Bretherick's, whereby concentration and heating during vacuum evaporation of a spent reaction mixture underwent accelerating decomposition (*9*, *10*). Decomposition on melting is known to be extremely exothermic (~1200 J/g at onset ~89 °C). Although more stable than other peroxy acids, pure *m*CPBA may detonate by shock or sparks and is therefore commercially available as a solid which is stable when refrigerated (nominally 72% *m*CPBA, 10% *m*-chlorobenzoic acid and water). Peroxy acids are also known to undergo metal catalyzed decomposition and therefore traces of transition metal ions from materials of construction or residual catalysts must be controlled and avoided.

In this case study, a large scale reaction involved the oxidation of a thioether to a sulfone (Figure 4). As the original medicinal chemistry step was performed in dichloromethane (DCM), there was a desire to replace this solvent from a volatile emissions perspective. Initially, replacement of DCM with toluene appeared to be a viable alternative: toluene is aprotic, widely applicable and its use would also facilitate telescoping into the following step. This reaction had already been carried out on a 1L scale and there was a literature precedence for thioether oxidations in toluene using *m*CPBA. There were no apparent safety concerns in either case (*11*, *12*).

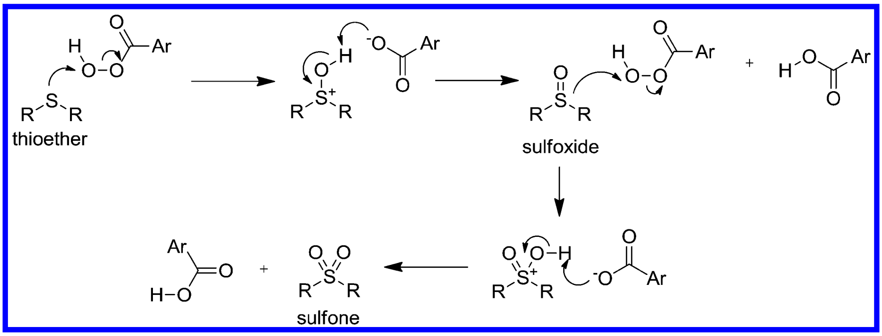

Figure 4. Oxidation of a thioether to a sulfone using a peroxyacid

However, routine safety evaluation by adiabatic calorimetry identified a violent runaway reaction with an onset of ~38 °C. The heat rate profile (Figure 5) was classic pseudo-zero order decomposition with an adiabatic temp rise of 119 °C. In addition, the pressure data indicated that gas evolution persisted for a considerable time after the exotherm had subsided. On opening the vessel, a carbonized 'honeycomb' remained in the test cell and no visible ejection from the vessel had taken place, implying that some of the contents had completely decomposed into gaseous products.

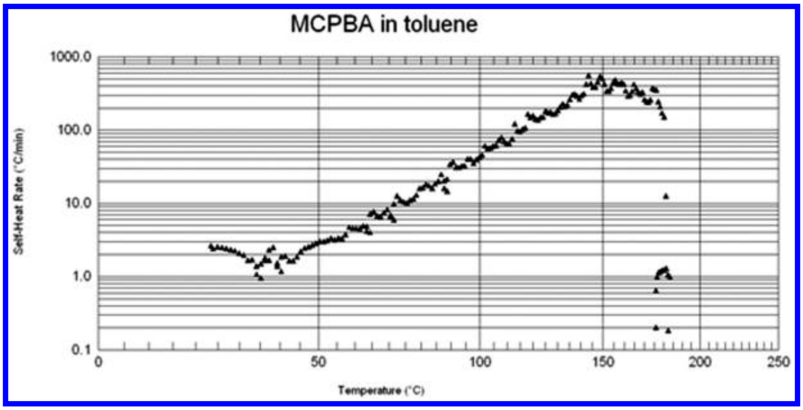

Figure 5. Self heat rate plot of mCPBA in toluene (log rate vs. 1/T)

Further investigation into published safety incidents involving *m*CPBA revealed that there was some evidence of its instability in certain media, most significantly an explosion in DMF (*13*). This adverse event was attributed to a trace impurity (0.2%w/w) in *m*CPBA – namely the diacyl peroxide *m*CPBO (Figure 6), which dissociated readily at fairly low temperatures and functioned as a free radical initiator for an oxidative chain reaction. Even following removal from *m*CPBA solutions by filtration, the paper reported that the peroxide impurity was readily regenerated when temperatures exceeded 25 °C.

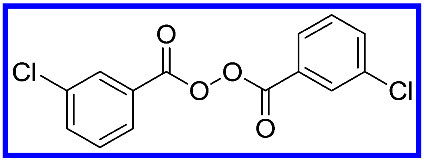

Figure 6. Chemical structures of peroxide impurity mCPBO

It was assumed that toluene had participated in propagating a free radical chain reaction through the formation of benzyl radicals under the influence of *m*CPBO (*14*). This reaction would initiate at fairly low temperatures. The reported (*13*) improved stability of mCPBA in DCM may in part be due to the solvent not participating in the propagation of the free radical decomposition of mCPBA. To assess the effect of metals, two further calorimetric runs were performed in DCM, one with a glass thermocouple and one with a Hastelloy thermocouple. The accelerating presence of metal ions was not proven conclusively and if anything, the absence of metals resulted in an earlier onset temperature. However, valuable conclusions related to the solvents did result. The levels of exothermicity and rate of off-gassing were much reduced in DCM when compared to toluene, as shown from the temperature-time profiles (Figure 7). The data from the three runs can be summarized in Table 1. Note that the data should be viewed merely within the context of a hazard screening tool. For example, the full extent of the exotherm in DCM was not observed due to tempering by boiling. This was an artifact of the experimental set-up (boiling point of DCM is ~165 °C at 320 psi). Also, the variation in delta H and activation energy, which are calculated based on the mole equivalents of mCPBA, disguises the potential variation in mCPBO levels in the test sub-sample. This example demonstrates that full knowledge of the test conditions must also be considered when making decisions based on hazard evaluation data.

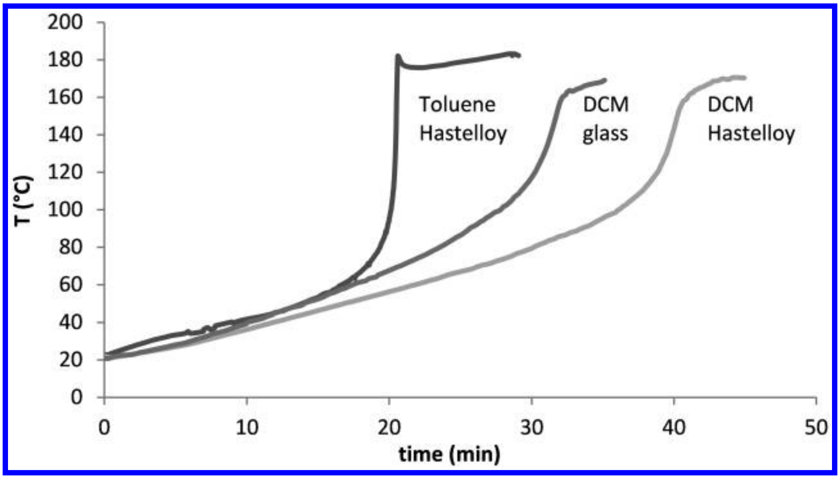

Figure 7. Temperature vs. time profile for mCPBA hazard experiments

Table 1. Hazard test data for mCPBA suspensions

Parameter	*Run 1*	*Run 2*	*Run 3*
Test solvent	Toluene	DCM	DCM
Thermocouple	Hastelloy	Hastelloy	Glass
Onset temp (°C)	45	60	37
Adiabatic T rise (°C)	119	>58[a]	>72[a]
Delta H (kJ/mol *m*CPBA)	-153	-73	-91
Apparent activation energy (kJ/mol *m*CPBA)	71	73	53
Temp of no return (°C) [b]	40	83	91
Max T rate (°C /min)	500	32	29
Max P rate (psi/min)	33	12	26

[a] The exotherm was tempered by boiling of DCM. [b] Estimated for 220L batch size in a 450L Hastelloy vessel.

At plant scale, the thioether solution in DCM was charged as a dose controlled addition to a pre-saturated *m*CPBA suspension in DCM at 25 °C, with tight temperature control. In this case, the increase in the TNR temperature limit, facilitated by the use of DCM as solvent, allowed the design of a reaction step which could be scaled up safely. As the reaction mixture was observed to thicken significantly during the addition, using the maximum rate of agitation in the plant vessel was the most important of these controls, in order to avoid potential accumulation of the thioether due to inadequate mixing.

In terms of developing a safe methodology for the use of *m*CPBA at scale, a recent publication (*15*) has reported the successful use of acetic acid as a solvent for a 28 kg input of *m*CPBA during an oxidation conducted at 55 °C. The ARSST data shown in that study suggested that the onset of decomposition was raised to 70-80 °C, with exothermicity similar to our results in DCM (-73 kJ/mol *m*CPBA). Control was established by dose control of mCPBA/acetic acid solution while maintaining batch temperature at 55±5 °C.

Another recent paper (*16*) reiterated the dangers of using *m*CPBA in a number of solvents, including DMF, DMAc, acetone and acetonitrile. The onset of decomposition during pressurized adiabatic testing similar to the ARSST was reported as 42-48 °C compared to the onset in DCM of 56 °C, which broadly agrees with our observations and previous studies. The authors of that paper report successful scale up to 8 kg input of *m*CPBA in DMF, albeit maintained below 10 °C and 13% w/w at all times.

This example demonstrates that the onset and intensity of a thermal hazard can be enhanced or diminished by presence of other substances; in the case of mCPBA, a peroxide impurity, solvent and contact with metals. The impact of impurities cannot be accurately predicted and therefore a systematic, experimental hazard evaluation using the actual lots of reagent intended for scale up is highly recommended. In addition, literature precedence for a procedure, even if reported multiple times, should not be accepted as a basis of safety for operation at any scale.

HCTU

The amide coupling agent 2-(6-chloro-1H-benzotriazole-1-yl)-1,1,3,3-tetramethylaminium hexafluorophosphate, (Figure 8) is better known by the abbreviation HCTU. Coupling reactions of high selectivity and conversion are of extreme importance in the synthesis of peptide as well as non-peptide molecules. A large inventory of nucleophilic catalysts is now available to enable these reactions. However, many of the early reagents were based on the 1-H benzotriazole motif, such as HOBt, and as a result have been shown to be explosive or have highly exothermic decomposition events (*17*). In many cases, amide coupling can be conducted at close to ambient temperature or without excessive heating and thus these reagents can be handled safely at scale with the usual best practice controls. HCTU has been hailed as an effective coupling reagent which is safe to produce and use, as it is reported as being non-toxic and non-explosive (*18*). However, problems may still be encountered, as described in the following case study.

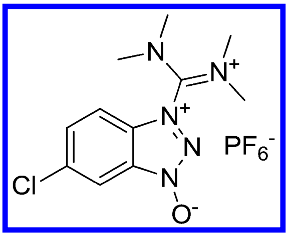

Figure 8. Structure of HCTU

A large quantity of HCTU was needed for a single campaign early phase project and was sourced cost effectively from a Far East supplier. However, on arrival the material failed a use test and elevated residual methanol content (~2% w/w) was identified as the cause. It was already too late to obtain an alternative source, therefore the process chemists devised an azeotropic drying step in the process solvent (toluene) to remove the methanol before proceeding with the synthetic step. As expected of these compounds, routine DSC analysis of the solid HCTU had shown a very sharp, energetic exotherm with onset around 190 °C. Although this may appear much higher than the maximum achievable process temperature (i.e. boiling point of toluene, 110 °C), DSC decomposition onset temperature can be a function of heating rate and the sample pan material. Rules of thumb relating to differences between the operating temperature and decomposition temperature should be viewed with caution and may lead to a false sense of security. There was sufficient concern that this adverse event could be reached during the rework and further investigations were performed.

Adiabatic calorimetry of HCTU in toluene did indeed show a major deflagration event at 163 °C but of more significance was the gentler exotherm masked by the endothermic activity between 80-100 °C (Figure 9). Lab experiments had shown that the HCTU develops a brown coloration at 100 °C. While this mild heating rate is barely visible in the temperature vs. time trace, it would be enough to raise the batch temperature to the deflagration point if there was a loss of cooling and agitation at plant scale. From the self-heat rate data, the batch size and knowledge of the reactor heat transfer properties, it was possible to deduce the time to maximum rate (TMR) at various temperatures. The industry standard for safe operation is TMR_{24hr}, in which there would be a day's efforts to re-establish control or develop a mitigation strategy. Frequently, it is not feasible to operate at the TMR_{24hr} as many chemical transformations would simply not occur at a reasonable rate. In order to stay well below the TMR_{24hr}, the batch would have been held at >47 °C and the methanol removed under reduced pressure and nitrogen flow, which was possible but prohibitively time consuming. A more rapid methodology was used successfully during the plant run to remove the methanol by distillation, in which the batch contents were maintained at ≤70 °C with upper limits placed on the maximum jacket temperature. If cooling was lost, manual operation of the bottom outlet valve to allow filtration of the batch was reserved as a protective measure.

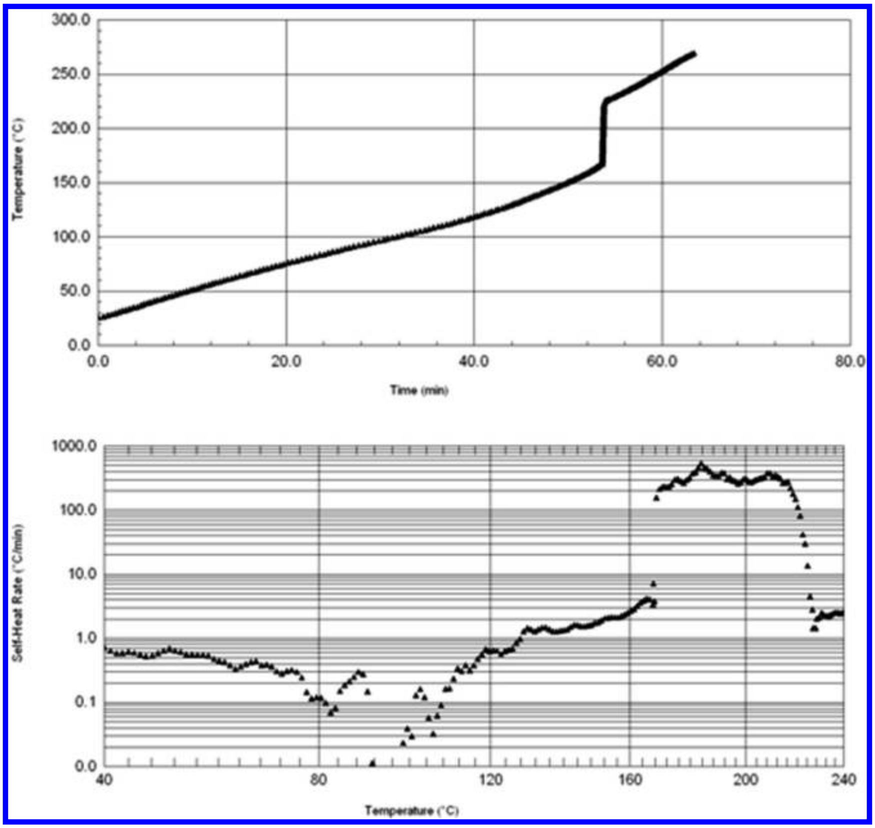

Figure 9. Temperature vs. time (top) and self-heat rate profiles for HCTU hazard run

In this example, the impurity was not directly responsible for the thermal hazard but its unexpected presence in a thermally sensitive reagent led to a potentially hazardous scenario. Therefore, in the absence of a systematic process of thermal hazard assessment, it is quite possible that this potentially damaging event would have been overlooked. It can also be inferred that a re-work scenario involving other benzotriazole core coupling reagents (HATU, HBTU, HOBt etc.) would exhibit the same hazard.

How the Reaction Is Performed Is Key to Controlling Hazardous Reagents

As already discussed, increasing scale results in the slower transfer of heat and gaseous by products from the reaction vessel. Therefore, the 'all-in' reaction, where all reagents and catalysts are charged and then heated to the reaction temperature, is regarded as an unsafe practice in most cases. All the exothermic potential is already present (i.e. 100% accumulation), the time to maximum rate becomes too short and the likelihood of a violent event becomes more likely. The hierarchy of control suggests that if the hazardous reagent cannot be eliminated or substituted, then engineering controls are the next best option. On scale up, this is most commonly addressed by semi-batch operation, i.e. dose control of one or more reagents into the other reagents, which are already maintained at conditions conducive to fast reaction. In fact, it is such a ubiquitous method of operation that during process development of a medicinal chemistry route for scale up, chemists should endeavor to transform any 'all-in' synthetic steps to semi-batch operation from the outset. Re-designing the mode of operation later in development can alter the impurity profile or product quality, as well as generate undesirable timeline and economic consequences. For fast exothermic reactions in which all of the reaction streams are solutions, operating in continuous mode is another option (*19*); heat and mass transfer are greatly improved and the volume of reaction mixture is maintained low enough to limit the damage resulting from any undesired event. However, design and implementation of continuous reactions is not trivial, especially for a single manufacturing campaign. Irrespective of which mode of operation has been selected, there can be unexpected complications arising from the use of certain hazardous reagents, such as in the two case studies outlined below.

Ethyl Diazoacetate (EDA)

Ethyl diazoacetate is primarily utilized as a reagent in homologation of ketones (*20*) and cyclopropanation (*21*) reactions. The hazards associated with this reagent are well documented, relating to significant issues with explosivity and shock sensitivity, even as a solution in toluene (*22*, *23*) or DCM. The onset temperature of an extremely exothermic decomposition is also sufficiently low to be easily accessed during reactions at scale (~50 °C for a 15%w/w solution in DCM) (*24*).

In one such example, the reaction of interest was a ring expansion of *N*-Boc-4-piperidone (Figure 10), which had been reported previously (*25*, *26*) as having shown dangerous accumulation, exothermicity and gas evolution when conducted in diethyl ether or DCM/MTBE. This was followed by a warning that the reaction should not be attempted at a scale of more than 1 kg in batch mode for safety reasons. For the campaign, it was necessary to perform a 5 kg batch and therefore highly likely that running the reaction in the same manner as the precedent would result in an adverse event.

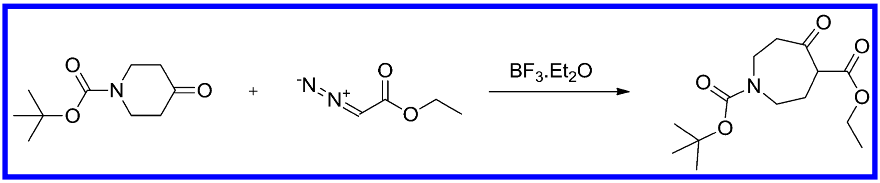

Figure 10. Ring expansion reaction using ethyl diazoacetate

The literature synthesis involved addition of $BF_3.Et_2O$ solution to a mixture of *N*-Boc-4-piperidone and ethyl diazoacetate dissolved in DCM/MTBE (1:4). ARC safety data obtained later reported the reaction to initially be very slow, attributed to an induction period, after which the reaction accelerated to a runaway scenario once 60% of the reagent had been added. The calculated adiabatic temperature rise (ATR) of over 45 °C would result in loss of containment at scale, if cooling or stirring control was lost. Scaling this reaction to kilogram charges safely in a conventional reactor was not recommended for this reason, which the authors of that paper addressed by successfully transferring the reaction to a small scale continuous process in a tubular micro-reactor.

An in-house hazard investigation was initiated to identify a suitable scale up strategy:

- Could the reaction be carried out continuously in a simple glass tube, potentially a coiled glass condenser?
- Could the reaction be performed in batch or semi batch mode? If so, what is the largest 'safe' batch size and what would be the safest way to achieve this?

Firstly, the thermal information was obtained from an ARSST run and checked against the reported data. The experimental set-up involved pre-cooling the two reagent solutions to -18 °C in a freezer to allow sufficient data to be collected on mixing in the test cell. In line with the reported values, the adiabatic temperature rise was at least 40 °C with considerable gas evolution and a very high activation energy of 211kJ/mol. This meant that slight increases in temperature would result in large rate increases and thus tight temperature control would be critical for safe operation.

Use of a simple rotary evaporator condenser was investigated as a reactor for direct scale up of the microreactor conditions, as this would deliver the required mass of product without the need to spend lab effort on re-development of the conditions. Using a residence time of 1.8 min (*25*) and the geometry of the inner coil of the condenser (4 mm i.d., length ~2.2 m, volume ~28 mL), it was possible to determine the heat transfer properties of such a system from established engineering design equations (*27*). Heat transfer was reasonably poor inside the coiled reactor due to laminar flow but accounting for cooling rates and various resistances, a specific heat flow value of 105 $Wm^{-2}K^{-1}$ was calculated. Although poor compared to a typical glass lined plant scale vessel (160-190 $Wm^{-2}K^{-1}$), this would be sufficient to cool the very small reaction volume, and the temperature of no return was estimated as 25 °C. In principle, the continuous reaction could be carried out behind a blast screen in a fume hood, albeit generating a modest but steady 70 g of product per hour.

Secondly, the case for a batch or semi-batch process was re-examined. There had been many protocols reported in patent literature for a batch process involving *N*-Boc-4-piperidone in diethyl ether, some of which involved simultaneous addition of EDA and an excess of $BF_3.Et_2O$ (*28*, *29*) but all had been conducted as small scale cryogenic reactions. The largest reported scale at that time (in 2008) was using 20 g *N*-Boc-4-piperidone, and had also been performed at the highest reported temperature (0 °C) (*30*). Subsequently, a 25 kg scale cryogenic reaction in ether involving simultaneous addition of EDA and $BF_3.Et_2O$ over six hours has been reported, without reference to any hazard assessment (*31*). However, from a scale up perspective, this approach is extremely hazardous due to the anticipated lag phase which would possibly lead to an uncontrollable runaway reaction. In batch mode, or during simultaneous addition of reagents at low temperature, the reagents would accumulate to generate a 'critical mass' in the reaction vessel. Any increase in temperature, by accident or design, would thus increase reaction rate, leading to the runaway. At a small laboratory scale, a temperature excursion might well go unnoticed due to the excellent heat transfer characteristics of small round bottom flasks. However, even at a fairly moderate laboratory scale (100 g), a runaway reaction could easily result and may lead to loss of containment and personal injury.

Upon closer examination of the chemistry it was not immediately clear why the transformation should require an excess of the $BF_3.Et_2O$ catalyst. It appeared that the reaction ought to be dose-controlled, i.e. that it ought to be possible to conduct the reaction safely by pre-mixing the catalyst and *N*-Boc-4-piperidone and using a dose controlled addition of the EDA, provided the reaction was sufficiently rapid (i.e. no accumulation). It was hypothesized that when using ethereal solvents, the substrate may have to compete with the solvent for the Lewis acid catalyst, hence the need for an excess and the sluggish start. By replacing the solvent with a non-coordinating solvent such as toluene, it was expected that the reaction could be controlled using the rate of addition of EDA to a mixture of the substrate and thus only a catalytic amount of $BF_3.Et_2O$.

An ARSST run was conducted involving a single charge of EDA into a mixture of catalyst (0.25 eq) and substrate in toluene, which had been pre-cooled to 5 °C. An immediate temperature rise of 35 °C occurred on mixing the two reactant solutions, implying that the basis of safety could indeed be rate of addition of ethyl diazoacetate. This represented a significant portion of the reaction enthalpy (ATR of 45 °C) and therefore the degree of accumulation during a controlled addition would be sufficiently low to permit the use of larger vessels. This chemistry was subsequently scaled up successfully in a cooled (but not cryogenic) 25 L reactor to produce 5 kg of the product in a single batch.

This example demonstrates that engineering controls improved heat flow and decreased reaction volume, and are valid solutions to the problems posed by hazardous reagents when it is not possible to ameliorate the risks through the chemistry alone.

Dimsyl Sodium (Sodium Methylsulfinylmethylide)

The utility of this reagent stems from the extremely weak acidity of DMSO (pKa = 35) (*32*), meaning that its conjugate base, the dimsyl ion, is an extremely strong base capable of removing protons from acidic carbons and thus finds application in formation of phosphonium and sulfonium ylides (*33*).

The formation of dimsyl sodium in neat DMSO is known to be extremely hazardous (*5*), leading to many examples of explosions and fires during the preparation of this reagent from the reaction with sodium hydride. At scale, the self-accelerated decomposition can occur at 50-60 °C, which was below the reported reaction temperature of 60-70 °C at laboratory scale (*34*). The source of the ferocious adverse event is the self-accelerating decomposition of DMSO. The dimsyl sodium reagent dramatically reduces the onset temperature, while the low volatility of DMSO (b.p. 189 °C) means that the runaway exotherm will not be tempered by reflux of solvent. However, a basis of safety was found for pilot plant scale up through dilution of the reaction with THF, as reported by Dahl et al (*35*). This paper suggested that ~0.4M Na dimsyl in a DMSO/THF mixture (1:6) showed an onset of decomposition at a higher temperature of 100 °C. As this was significantly higher than the boiling point of THF (67 °C), the heat of dimsyl sodium formation could be dissipated at reflux without accessing the decomposition.

This latter development in the use of dimsyl sodium prompted an in-house process improvement program. A reaction step had been developed using the related reagent lithium dimsyl and had been carried out successfully for twelve campaigns at up to 50 kg batch size. Lithium dimsyl is prepared in situ from butyl lithium and DMSO. With demand for the product increasing, the cost of goods at larger scales was becoming prohibitive. Salt metathesis of Na dimsyl using LiCl in DMSO/THF was investigated as a means of scaling up this reaction safely, while lowering the cost of goods by using sodium hydride instead of butyl lithium, as shown in Figure 11.

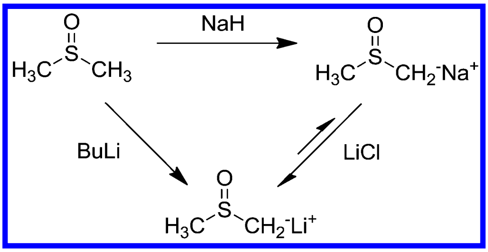

Figure 11. Schematic illustrating the preparation of lithium dimsyl

A series of ARSST runs were conducted for lithium and dimsyl sodium at the usual overpressure of 20 bar of nitrogen. The temperature vs. time profiles in Figure 12 show that the thermal behavior varies greatly with concentration and counter-ion. An explosion occurred at 103 °C for the 2.4 M solution and demonstrated the dangers of operating at high concentrations, regardless of counter-ion. For 0.6M dimsyl sodium, a gentle exotherm (also onset at 103 °C) led to a sharp but short-lived temperature spike. The same concentration with lithium had a lower onset of ~70 °C but an equivalent intensity and onset of gas evolution (ATR of 25-28 °C and ~67 °C respectively for both counter-ions). This initially implied that dimsyl lithium was safer than the dimsyl sodium, as it would be easier to maintain or re-establish process control during an adverse event with no sharp exothermic events expected.

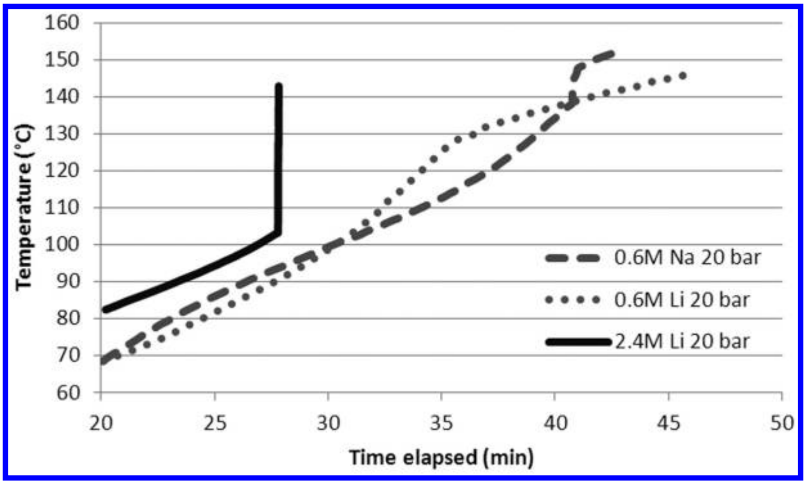

Figure 12. Temperature vs. time plot during hazard test runs at 20 bar

However, it is very important to relate the data obtained during a hazard test to ‘real life’ scenarios. In a case such as this, it is good practice to re-run adiabatic calorimetry at a lower backpressure, preferably the bursting disk pressure of the intended plant vessel, as this will mimic the actual temperature and pressure profiles during a runaway at scale. Surprisingly, running the 0.6 M dimsyl lithium experiment at 4 bar resulted in a lower decomposition onset of 45 °C along with significantly higher maximum heat rate, activation energy and heat of reaction (Figure 13). The decomposition mechanism for DMSO is not known conclusively but does involve gaseous by-products, which can propagate further exothermic side reactions (*36*).

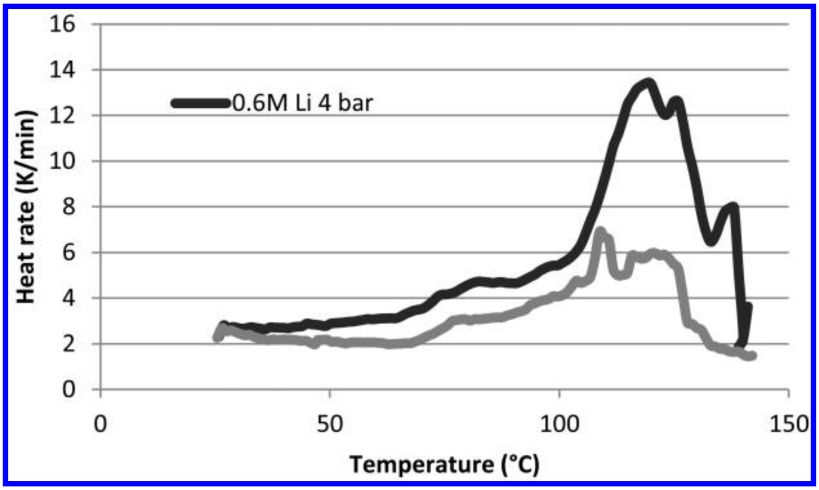

Figure 13. Pressure dependence of self-heat rate of 0.6M Li dimsyl in 1:1 DMSO:THF

For this example, it was clear that the lower dimsyl lithium concentration was feasible but would require further detailed hazard evaluation to implement the salt metathesis process. From a risk and cost-benefit analysis, we did not pursue this program and retained the existing process with butyl lithium.

It is recommended that for the scale up of dimsyl sodium reactions that the concentration of the reagent be kept as low as is feasible (≤0.6 M), especially through the dilution of the DMSO with a co-solvent like THF. Higher concentrations (~2 M) and storage of any concentration of dimsyl solution should be avoided or thoroughly risk assessed.

From this example, it is clear that the hazard methodology employed can generate misleading results unless the underlying chemistry is thoroughly understood. Where hazardous events are suspected from intial testing, it is recommended to retest using conditions which mimic plant operation more closely. As it is very difficult to predict what will impact operational changes may have, it is best to 'expect the unexpected' and perform additional tests. In the custom synthesis business, sometimes the reaction 'just has to be run' with minimal changes due to cost and time pressures. However, safety should not be compromised. In these circumstances, the hierarchy of control is a useful tool in the development of a safe process at scale.

Quenching the Reagents Can Present More Problems than the Reaction

As highlighted above for the unexpected impact of impurities, the quenching of mature reaction mixtures can be overlooked in hazard assessment but show a much higher potential for adverse events. The reactions involved tend to be simple, such as acid/base neutralizations, but can be quite exothermic and frequently evolve gases (e.g. CO_2 from bicarbonate washes, hydrogen from hydrides, or HCl from chlorinating agents). The reactors also tend to be full as all reagents have been charged, which is the worst case scenario for disengagement of gases, thus increasing the risk of a loss of containment through foaming, batch swell or entrainment of batch contents during venting (two phase flow). We will discuss some reactive reagents that led to problems.

Acetic Anhydride

Acetic anhydride is widely used in acetylation reactions. This reagent is usually quenched during work-up with water, methanol or ethanol. Although the hydrolysis of the anhydride appears straightforward, this reaction can become violent at scale as it is autocatalytic (acid catalyzed). The hydrolysis rate can be particularly variable as the temperature, agitation, order of mixing and proportion of water (which is immiscible at some ratios) are instrumental in maintaining and controlling heat generation. The presence of catalytic impurities such as acidic salts is therefore a major concern and has resulted in industrial accidents involving acetic anhydride (*37*).

In a recent example, plant production was nearly delayed because hazard assessment on an acetic anhydride quench (Figure 14) required a more thorough investigation following a HAZOP meeting. The quench involved the ethanolysis of residual acetic anhydride at 45-50 °C; at lower temperatures the reaction mixture became viscous due to the crystallization of product. The process had already been investigated elsewhere using calorimetry, but the test was conducted at a higher temperature (85 °C). Suspicions were raised at the follow-up HAZOP by the higher operating temperature for the hazard test (which would mitigate accumulation of reagent and was also above the boiling point of ethanol) and a lower than expected value for the heat of reaction (which ranges from about -58 kJ/mol anhydride for hydrolysis (*38*) to -67 kJ/mol anhydride for alcoholysis (*39*)).

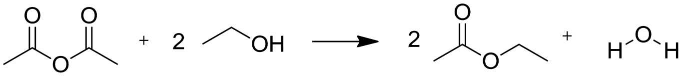

Figure 14. Ethanolysis of acetic anhydride

From an ARSST run of the quench, it was possible to calculate the heat of reaction as -66.5 kJ/mol anhydride and activation energy as 49.8 kJ/mol respectively. The latter agreed with literature values of 46-48.5 kJ/mol (*40*, *41*) and the results confirmed that the hazard test had gone to completion. Using this data and as the literature reported a pseudo-first order rate constant (*42*) of 0.00061 min^{-1} at 25 °C, it was possible to model a 5 L scale quench for which reaction profiling had already been monitored by the development chemists. It also revealed that the quench progresses slowly, even at 45 °C (anhydride half-life: 321 min) in contrast to a 39 min half-life at 85 °C. Addition of ethanol at 45 °C was therefore having a limited impact on anhydride level and the quench could not be truly dose controlled at this temperature.

However, as is often the case for pharmaceutical intermediates, the use of temperatures exceeding 60 °C was shown to compromise product quality and was deemed a practical upper limit to the quench temperature. In the proposed quench at 45-50 °C, two hazardous scenarios were therefore envisaged; accumulation of all the ethanol due to a stirring failure or phase separation (i.e. inhomogeneity), or a loss of cooling after addition of all the reagents. Both scenarios could effectively be addressed by considering an adiabatic runaway 'all-in' reaction.

At the intended scale, the total batch size was 227 kg, allowing calculation of the heat transfer area and active cooling rate at this fill level (1.44 m^2 and 190 W/m^2 respectively). The temperature of no return for the 'all-in' reaction (100% accumulation) was calculated at 58.7 °C using this data, which at first glance is uncomfortably close to the fairly ineffective operating temperature of 45-50 °C. Nonetheless, assuming the worst case of adiabatic conditions during cooling failure, the energy released from the contents at this scale would have been 29.4 MJ, some of which would be absorbed by heating the contents to the boiling point of ethanol (78 °C) and the rest dissipated through the latent heat of vaporization of the ethanol, or the generated ethyl acetate, during reflux. In this worst case, around 15 kg of the solvent would vaporize before the exotherm would burn out, which would be easily handled by leaving the vent line to the condenser open. As an extra precaution, addition of more ethanol at ambient temperature was also considered in the event of a loss of cooling. The cooling and dilution effect of adding more ethanol would decrease the amount of vapour lost to the vent line.

Although not an ideal solution, the 'fail safe' of solvent tempering allowed a basis of safety to be found for running the reaction at this scale. Upon significant depletion of the anhydride after stirring below 50 °C for several hours, the reaction temperature could be increased slightly to pass the in-process control test limit of >1% anhydride within an acceptable timeframe without compromising product quality.

As Pharma projects progress through the clinical phases, the manufacturing process becomes increasingly locked due to regulatory constraints. Therefore, there may be a temptation to unconditionally accept hazard assessments conducted in earlier phases due to the lockdown of the process. This example demonstrates that process safety should be re-examined regularly throughout development. For this process, which was already in late phase, the flexibility for changing reaction conditions was greatly reduced; catching the problem earlier may have allowed for a more elegant or cost effective solution, while still addressing the hazard.

The authors would point out that this example emphasizes the need for holistic process design from an early stage of chemical development, which does not solely focus on product quality but also incorporates control of process hazards as a key success criterion.

Phosphoryl Chloride ($POCl_3$)

This reagent is primarily used in the formylation of aromatics (Vilsmeier-Haack reaction (*43*)), as a phosphorylating agent, and a chlorination agent, particularly in the dehydroxychlorination of heteroaromatics (*44*). Due to a difference in reactivity, only one of the P-Cl bonds is utilized effectively in synthesis, with the result that the remaining two bonds must be hydrolyzed during the quench, (Figure 15). Numerous examples have been reported of uncontrolled exothermic events during hydrolysis, which are sufficiently violent to generate steam and evolve HCl gas (*5*). The problem stems from the slow hydrolysis rate and high activation energy (i.e. strong temperature dependence) of the principal waste product, phosphorodichloridic acid. An excellent investigation into kinetics and safety assessment of $POCl_3$ hydrolysis has been published by Achmatowicz et al (*45*).

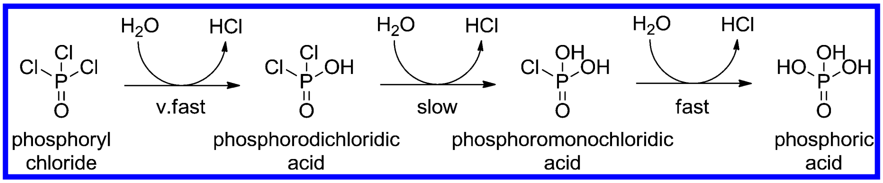

Figure 15. Schematic of the hydrolysis of phosphoryl chloride

Normally, on completion of the reaction involving phosphoryl chloride, the reaction mixture is added into cooled water or a dilute base solution (note: it is safer to use basic phosphate solutions in this instance, e.g. trisodium phosphate). The danger is that the instantaneous hydrolysis of the first P-Cl bond is mistaken for a sign of reaction completion and the mixed organic/aqueous waste is transferred to drums for treatment prematurely. Due to the relatively high activation energy (~74 kJ/mol), a slight increase in temperature produces a larger increase in rate than might be expected. Put another way, the rate will double every 5-6 °C, which is significantly faster than the 'rule of thumb' of 10 °C. Therefore, through self-heating during storage, considerable pressure can be generated in the drum, leading to rupture and release of corrosive waste.

The case study relating to phosphoryl chloride is shown in Figure 16 and relates to dehydroxychlorination of a heteroaromatic. In this case, the addition of the reaction mixture into large amounts of water, or vice versa, resulted in the precipitation of the product as an unfilterable mass. Cooling the reaction mixture to lower temperature without addition of water did result in crystallization but with greatly reduced yield. Therefore, post reaction treatment of mother liquor would not address the problem as further recovery of product during this additional step would still be necessary .

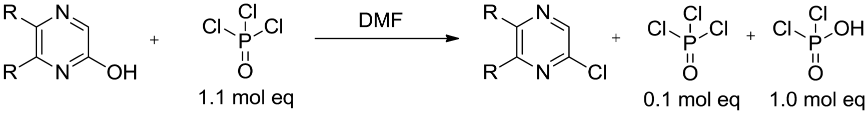

Figure 16. Dehydroxychlorination of heteroaromatic using phosphoryl chloride

Guided by the kinetic data available (*45*), 60 °C was the optimal temperature to allow rapid hydrolysis of the remaining phosphorodichloridic acid with 'just enough' water (1.1 eq with respect to P-Cl bonds). As is often the case, it is better to maintain control over a hazardous reaction step by speeding it up (i.e. running at higher temperature) rather than prolonged quench at low temperature, due to the dangers posed by accumulation. At 60 °C, the product was in solution and the water used to quench the residual P-Cl bonds also conveniently acted as an antisolvent to nucleate the product, which was isolated in >90% yield on cooling. This example demonstrates that the quenching of hazardous reagents may seem trivial but factors such as varying kinetics, auto-catalysis and precise measurement of quench volumes can become important. The serendipitous result of the water quench also functioning as an antisolvent demonstrated that the quench does not have to be a separate problem to overcome but can be integrated into process design to deliver inventive solutions.

Conclusion

The safe management of hazardous reagents is a critical part of the transition from medicinal chemistry to pilot scale processes. Given the demands of time and budget in early phase campaigns, it is important to have a systematic and robust methodology for hazard evaluation to reduce the time required for these examinations without compromising safety.

Nonetheless, adverse events related to hazardous reagents do occur, despite concerted efforts by the industry to eliminate them. Therefore, it can be inferred that the root causes of these unexpected events were unforeseen by solely reviewing the desired chemical transformation or operational step. As demonstrated in the first two case studies, it is always necessary to test for thermal hazards on the actual raw materials (i.e. a 'use test') as part of a development and scale-up program. However, testing should not solely be relied upon to generate the basis of safety, as it is not possible to explore all possible eventualities or indeed design appropriate experiments to test them. A paper based brainstorming approach (e.g.'what if?') to identify the impurities or contaminants with highest probability and/or severity of adverse events is recommended prior to testing to maximize the chances of detection and prevention. To this end, it is important to write fully balanced chemical equations to include all of the by-products as well as hypothesize alternative reactions that may occur from impurities or other sources.

The remaining case studies illustrate the importance of 'holistic process design', where the integration of hazard reduction measures and the maintenance of product quality should be viewed with equal importance. All of the examples clearly demonstrate that there is a need to think about the chemistry when considering the scale up of hazardous reagents. In particular, during the desired reaction, the impact of exothermicity or gas evolution, the effect of contaminants and impurities, how the reaction is performed and how it is quenched. At first glance, this approach may appear to be more laborious (and thus expensive) but the authors would argue that it is an opportunity for process chemists to demonstrate their skills and creativity, generate valuable intellectual property, and avoid incidents leading to environmental and personal injury. Indeed, it is this expertise to scale up safely and efficiently which defines process chemistry as a challenging and stimulating discipline in its own right.

Acknowledgments

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Chapter 9

Development of a Multi-Kilogram Procedure To Prepare, Use, and Quench Ethyl Diazoacetate

James H. Simpson,* Atul S. Kotnis, Rajendra P. Deshpande, David J. Kacsur, Jason Hamm, Gus Kodersha, William Merkl, Daniel Domina, and Steve Y. Wang

Chemical Development, Bristol-Myers Squibb, One Squibb Drive,
P.O. Box 191, New Brunswick, New Jersey 08903-0191
***E-mail: james.h.simpson@bms.com**

A practical, high yielding procedure for the efficient preparation of toluene solutions of ethyl diazoacetate (EDA) from ethyl glycinate is described. The process incorporates extensive safety studies related to the preparation and handling of a carcinogenic and explosive reagent. In addition, a safe neutralization process for the excess EDA and waste streams were developed. EDA was successfully made as a solution in toluene from three 175-kg batches of ethyl glycinate.

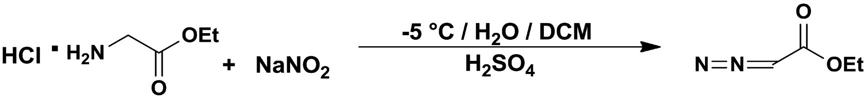
Introduction

Ethyl diazoacetate (EDA) is a versatile reagent commonly used as a source for carbenoid species in metal catalyzed cyclopropanations such as the Simmon-Smith reaction (*1–3*). It has found other applications in the synthesis of furans (*4*), ring expansions of cyclic ketones (*5–7*), homologation of esters (including synthesis of propargylic esters) via reaction with alkyl boranes (*8*, *9*), and 1,3-dipolar additions to 1,4 quinones (*10*). EDA is a high boiling yellow liquid which is highly toxic (acute oral lethal dose up to 5 mg/kg), a carcinogen (*11*), and explosive. EDA will explode upon heating and ideally should be handled below 50 °C. The thermochemical properties were explored by reaction calorimetry for manufacturing scale-up (*12*). Decomposition of EDA via dimerization with the evolution of nitrogen gas is rapid and exothermic when catalyzed by certain metals or metal-salts (such as Cu and Zn), and hence EDA must be handled with ***extreme caution*** to avoid inadvertent trace metal catalysis leading to an exothermic decomposition with gas evolution or explosion. Clearly this is not a trivial compound to make or handle, particularly on larger scale.

In connection with one of our projects, the need arose to prepare large quantities of EDA and use it in a subsequent reaction (*13*, *14*). Even though EDA is available commercially (*15*), it cannot be obtained in bulk quantities for synthesis because of the risks associated with transporting an explosive substance. Hence a fit-for-purpose process to prepare EDA on scale for use in our process was developed. Our goal was to build upon this work to enable the preparation of 100 kilogram batches of EDA in solution at a pre-determined concentration range, so that it could be immediately used in the next reaction without any further manipulation (e.g. distillation). In order to conduct such chemistry safely in the plant, a careful review of the thermal properties of the intermediates, reaction mixtures, EDA, and side-streams would be required. We describe in this manuscript our process development of the chemistry, our safety investigation that permitted entry into the plant, and a large scale campaign that met all our goals.

Discussion and Results

Initially, EDA was synthesized in the laboratory, according to the literature procedure starting with ethyl glycine hydrochloride in 79-88% yield (*16*). Ethyl glycine hydrochloride was diazotized with sodium nitrite and sulfuric acid at -5 °C in methylene chloride (DCM) (Scheme 1). The exothermic reaction evolved NO, NO_2, and N_2 gases as side-products and was completed over 10 min, as indicated by the decrease in heat evolution and a negative starch-iodide test indicating the absence of nitrite ions (*17*). The starch-iodide test was a rapid and convenient in-process control for indicating the end of the reaction. As the EDA formed, it was continuously extracted into the methylene chloride phase, thereby minimizing exposure to acidic conditions which would decompose EDA. EDA can be further purified by vacuum distillation at b.p. 29–31 °C/5 mmHg; however, use of the “as is” solution directly from the work up protocol was a prerequisite for the down-stream chemistry we required. Having evaluated the current procedure, process development suitable to our application and resources started from this point.



Scheme 1. Organic Syntheses route to EDA

The first modification to the existing procedure was to replace sulfuric acid in the biphasic reaction solution with a mixture of acetic acid and sodium acetate to provide a buffered system with a pH of 4.5. This was beneficial as the aqueous mixture of the ethyl glycinate hydrochloride and sodium nitrite alone results in a solution of a pH of ~ 5.0 within which range the nitrous acid only slowly initiates the diazotization process. Decreasing the pH to 4.5 increased the reaction rate. Buffering the system gave us a tighter pH range to maintain control the reaction rate and the heat generation at an acceptable rate during the diazotization reaction. However, the solubility of acetic acid in methylene chloride defeated the concept of isolation of the sensitive product and substantially decomposed the newly formed EDA. While deleterious to our process, this propensity was later used to our advantage to decompose EDA and neutralize unused material in a controlled manner (see work up section). However, a new buffer system was still needed for a useful process.

The use of sodium borate as a buffer component for the preparation of EDA has precedent (*18*), but initially we wished to understand what buffer composition could shut down the reaction. Sodium borate decahydrate added to the aqueous solution of ethyl glycinate and sodium nitrite produced a 3.6 M solution of pH ~ 5.3, a level where the diazotization reaction was still not completely suppressed. More sodium borate was added until the pH remained constant at > 6.0 to completely suppress the diazotization reaction (*19*). The ability to control the start and the rate of this potentially explosive reaction was critical for large scale preparation. Borate buffer was chosen as a versatile aqueous phase to which adding dilute H_2SO_4 (described later) initiates the reaction, allowing full control of reaction kinetics.

We also sought to replace the reaction solvent, as DCM was no longer a viable alternative in consideration of the acetic acid miscibility leading to EDA decomposition. A second disadvantage was that the work-up of EDA prepared in methylene chloride posed a significant handling problem of manipulating a rich-bottom phase on scale because it involves discharge of both phases in order to discard the upper aqueous phase followed by recharge of the organic phase for further work. MTBE (*20*) and toluene were both successful replacements. But toluene had the advantage that it provided a greater heat sink due to its higher boiling point in the event of an exothermic excursion. Initially, EDA was prepared in both MTBE and toluene and produced comparable yields and quality, but MTBE was shown to be unsuitable in the subsequent chemistry and further chemistry was conducted in toluene alone.

We broadened the reaction temperature range from 0-5 °C to 5-20 °C to permit additional latitude for processing on large scale as no deleterious effects resulted. The addition of dilute sulfuric acid lowered the pH to 4.5, initiated the reaction which was exothermic, but addition control was utilized to maintain the temperature between 5 and 20 °C. Under these conditions, slow addition of 2 wt% H_2SO_4 to the buffered media led to complete conversion to product. Controlling the rate of pH change controlled the reaction rate and decreased the amount of decomposition.

In addition, the amount of sodium nitrite was reduced from 1.50 to an optimum level of 1.05 equivalents. Reducing the charge of sodium nitrite increased the safety factor by decreasing the NOx gas evolution without decreasing either the yield or quality. Combining the changes of solvent, temperature, stoichiometry, buffer, and pH control afforded 85 - 90% overall yield of EDA . The product solution obtained by this process consisted of the required purity, impurity profile and concentration for the subsequent carbenoid addition chemistry.

Third Generation Process

Sulfuric acid is a common reagent but it is a hazardous substance for use on scale due to operator exposure and environmental hazard. While we had the option, we sought to replace it with a safer alternative. Subsequent optimization led to the replacement of sulfuric acid with 2% phosphoric acid. In this instance, EDA was prepared by controlled addition of 2% phosphoric acid to a well mixed biphasic reaction mixture in toluene and water to initiate the formation of the diazo intermediate. For maximum volume efficiency in the EDA preparation and for the correct concentration in the subsequent chemistry, the ratio of the glycinate salt charged to the final reaction volume (water, toluene and 2% phosphoric acid) was optimized at 1:10. Modulation of the reaction exotherm by the controlled addition of phosphoric acid to keep the batch temperature between 5 and 20 °C and the pH at 4.5 to 5.0 generated the optimal reaction rate.

For the work up, aqueous sodium bicarbonate washes afforded EDA rich-toluene streams possessing $\leq$ 0.25% water, pH $\geq$ 5.5, and a concentration range of 0.2 to 0.3 mg/mL, all in line with requirements for the subsequent reaction. The desired concentration was achieved by refraining from the use of additional toluene during the aqueous work-up. React-IR studies indicated only trace hydrolysis of the product during diazotization and no ester hydrolysis or product decomposition was observed after the sodium bicarbonate work-up.

The overall yield of EDA produced in this manner was 85 - 90 %. Approximately 5 mole % of the EDA was lost to aqueous washes as a result of the partial solubility of toluene in water (*21*). These solutions were only briefly stored prior to reacting them in subsequent chemistry. This process was directly scaled into our pilot plants to prepare 128-130 kg batches of EDA in solution in reproducible 90-91% yields without any incident or other changes in the protocol (Table 1). These solutions were only briefly stored prior to reacting them in subsequent chemistry.

Table 1. Plant batches of EDA preparation

Wt Input of Glycine ester (kg)	*Moles of Glycine ester*	*Wt Output of EDA (kg)*	*Moles of EDA*	*% Yield*
174	1250	130	1137	90.9
175	1254	130	1141	91.0
175	1254	128	1121	89.5

Safety Issues Related to EDA and Neutralization of Unused EDA and Waste Streams

The preparation of EDA from ethyl glycinate hydrochloride is an exothermic process. The heat of the reaction is approximately 280 cal/g of glycinate salt, but well controlled by the rate of addition. The observed adiabatic temperature rise was 33 °C, which is not unusually high; but in consideration that EDA may energetically decompose at > 50 °C, there was concern that we confirm the latitude the process possessed for processing.

A 90 wt% solution of EDA containing residual DCM was tested and shown to be insensitive to mechanical impact. However, friction testing demonstrated positive results at a force of 40 Newtons. This indicated that precautions should be taken for charging EDA and contingencies should be established for cooling. In the optimized process, the heat evolution rate can be controlled by the phosphoric acid charging rate and active cooling. The friction concern was addressed on scale by pressure transfers thereby avoiding the use of pumps which could possibly cause friction and a potential explosion of the solution.

The exotherm generated during the 0 – 5 °C EDA preparation was immediate upon addition of the acid to the bi-phasic mixture of glycinate and sodium nitrite, a welcome observation since it implied no accumulation of reagents was likely. To examine worst case scenarios, 2 wt% phosphoric acid was added at 0 °C over 1.0, 1.5 and 2.0 h while monitoring the reaction by React IR. (Figure 1). Charging the acid over 1 h resulted in the maximum observed temperature of 44 °C. The slowest addition, 2 h, well controlled the exotherm and led to a temperature rise of only 35 °C. The plant reactor chosen for this chemistry, its size, configuration, and heat transfer package was well suited for handling an exotherm generating 50 watts/L, and thus a 2 h addition time where the maximum heat was 35 watts/L was determined to be within a safe operating range.

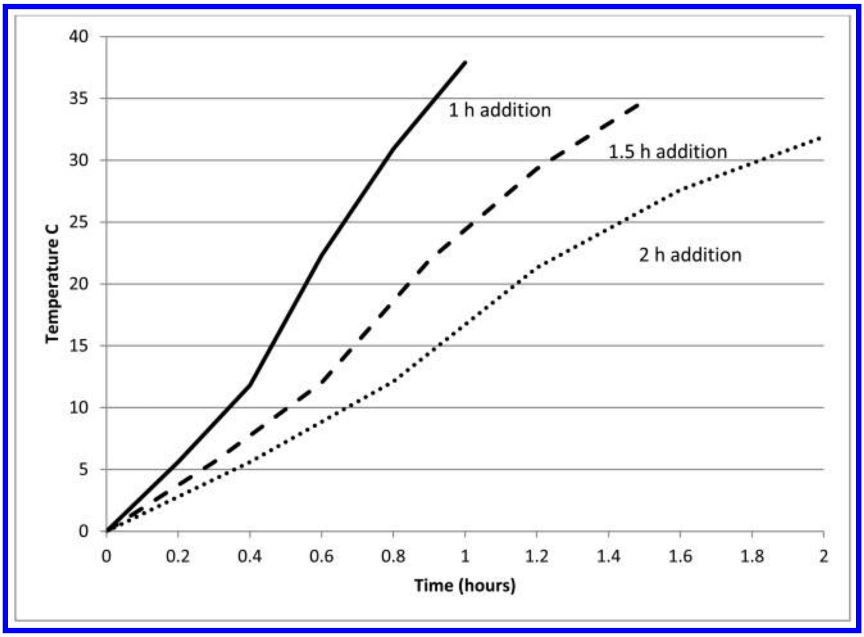


Figure 1. React IR traces for addition of 2 wt/wt% phosphoric acid to the reaction mixture.

RSST (Reactive System Screening Tool) studies were performed on a 90 wt% EDA (*22*) containing DCM to identify if any thermal event occurred upon heating and to what magnitude. Heating a 5.0 mL sample at 0.5 °C/min to 160 °C under 300 psig of nitrogen resulted in self-heating at 85 °C increasing rapidly to 100 °C with a sudden pressure surge. The RSST cell was completely shattered during this event, underlining the challenge in designing a safe process.

An ARC (Accelerating Rate Calorimetry) study produced the following information:

Observed initial reaction temperature	80 °C
Maximum self-heat rate	> 500 °C / min. (exceeded instrument data collection)
Maximum pressure	2000 psig
Calculated adiabatic temperature rise	500 °C
Decomposition energy estimation	250 cal /g
Time to maximum rate at 100 °C	25 min

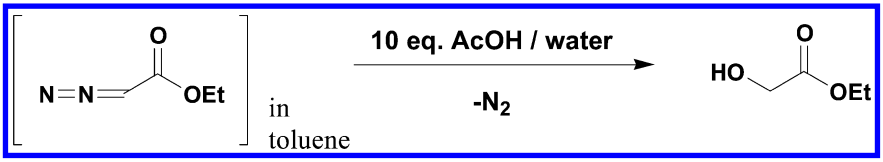
Clearly EDA decomposition would be very energetic.

We also examined the impact of metallic impurities using a Carius tube; useful for screening materials or mixtures for thermal hazards. It is generally employed for preliminary identification of exothermic reactions or gas evolution when the sample or mixture is exposed to elevated temperatures. Copper sulfate powder was added as a 2 wt% concentration to 5 mL of 90 wt% EDA held at 35 °C. As the sample temperature neared 40 °C there was a rapid exothermic event which produced enough pressure to shatter the Carius tube (maximum recorded pressure was 25.4 bar). The 90 wt% EDA sample was also tested to examine the possibility of rust (iron oxide) catalysis of a hazardous event. No evidence of self-heating or gas evolution was observed under the conditions studied. However, the results of the copper catalyzed decomposition require that maximum precautions be taken to exclude likely catalysts of EDA decomposition.

Work Up Considerations for Preparing EDA

As part of the hazard evaluation, a safe quench procedure was required for disposal of excess EDA solutions in the subsequent chemistry. An earlier observation regarding the decomposition of EDA with acetic acid led to a useful neutralization process by addition of EDA to 10 eq. of a 50 wt/wt% acetic acid in water. This treatment safely produced ethyl hydroxyacetate which was non-hazardous and safe to dispose using ordinary procedures (Scheme 2). Gas evolution was addition controlled under these conditions. Phosphoric acid was also effective, however it led to uncontrolled gas evolution.

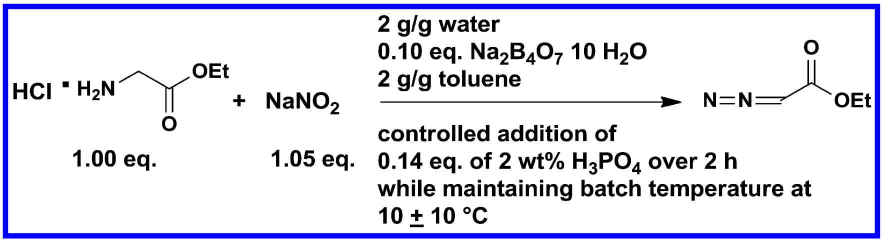
Treatment of the aqueous waste streams was necessary due to the amount of residual EDA and sodium nitrite presenting hazards for waste handling. The aqueous waste streams were treated with 20 wt% phosphoric acid to decompose the remaining EDA. The treatment procedure was to charge the aqueous waste to the phosphoric acid at a controlled rate to maintain temperature and off-gassing at an acceptable rate. However, the sodium bicarbonate waste washes were not treated in this manner as extensive carbon dioxide gas would have been generated. They were examined by RSST and no self-heating or gas evolution was observed. While some EDA was present, it was determined that the level was low enough that it was unnecessary to further treat these washes. These as well as the neutralized aqueous waste streams were placed in plastic lined drums and disposed of as ordinary hazardous waste. Development of safe means to clean up these reaction side-streams and remaining solutions completed our work in developing a multi-kilogram process to prepare and use ethyl diazoacetate



Scheme 2. EDA quenching reaction with acetic acid

Conclusions

A controlled and practical procedure (Scheme 3; Figure 2) to prepare EDA in toluene on a large scale was developed within guidelines that permitted bringing this chemistry into the plant to prepare 130 kg batches of EDA. The resulting toluene solutions required no further treatment and were successfully telescoped "as is" into the subsequent reactions. An array of safety investigations established the parameters that permitted safe operation at these levels.



Scheme 3. Controlled formation of EDA

Experimental Section

General

Potency of vendor supplied ethyl glycinate hydrochloride was 99% (^{1}H NMR analysis). The diazotization reaction proceeds to complete conversion of the ethyl glycinate as indicated by a negative starch iodide paper.

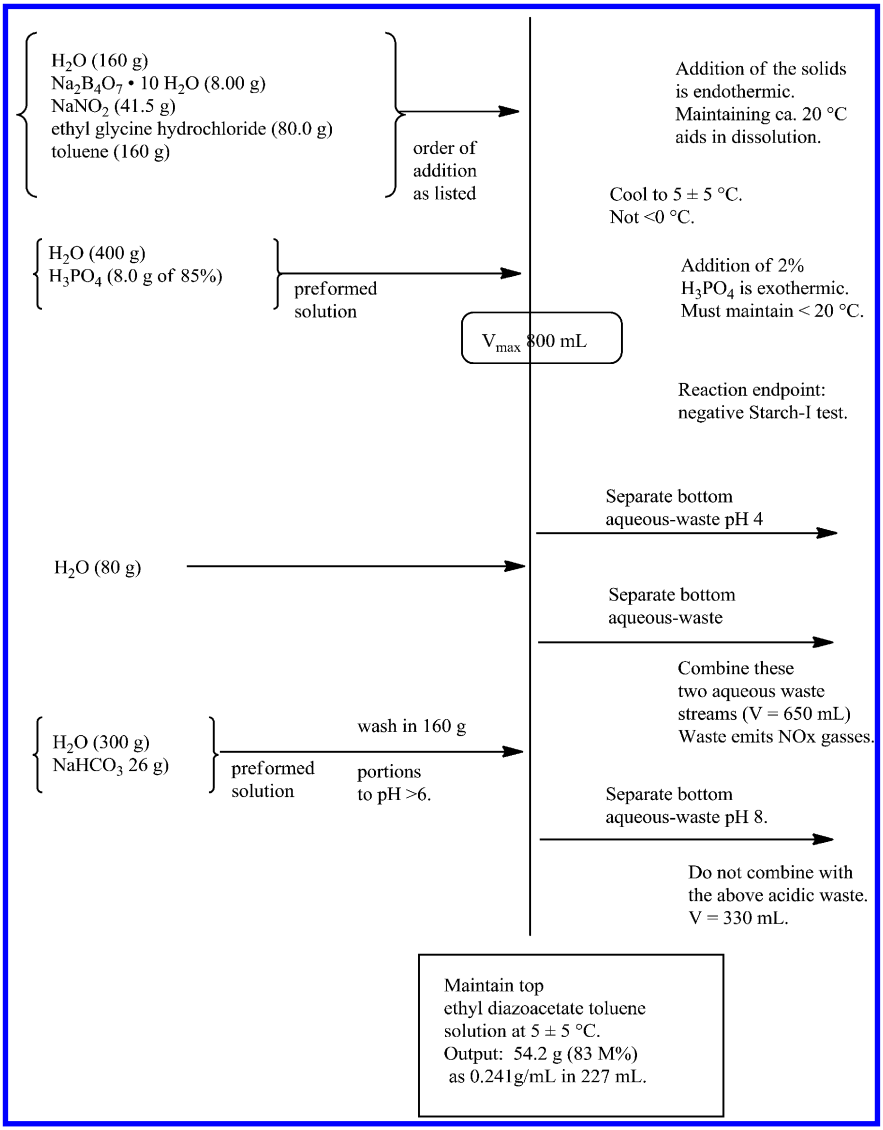


Figure 2. Process Flow Diagram for the preparation of EDA

Pilot Plant Preparation of Ethyl Diazoacetate Solution in Toluene

A 500 gallon Pfaulder glass-lined reactor was equipped with a thermocouple, pH electrode, an inlet for controlled addition of phosphoric acid and a nitrogen purge connected to a thermal oxidizer. Charge water (350 kg) to the reactor, followed by sodium tetraborate decahydrate (17.5 kg, 45.9 mole, 0.10 eq.) . Agitate at ambient temperature to dissolve as much of the solids as possible. Add sodium nitrite (90.8 kg, 1315.9 mole, 1.05 eq.) , followed by ethyl glycinate hydrochloride (174.4 kg, 1249.5 mole, 1.00 eq.). Agitate the contents of the reactor until dissolution is complete. The resulting aqueous solution has a pH of 6-7. Add toluene (350 kg) to the reactor. Cool the bi-phasic mixture to 0 – 5 °C. To the bi-phasic mixture charge 2% phosphoric acid (889 kg) over 2 h, at a rate (~7.4 kg/min) at <20 °C. Maintain the reaction mixture at 10 ± 10 °C until the reaction is deemed complete. This is defined when the pH drops to 3.5 to 3.74, a sample of the aqueous phase turns starch-iodide paper blue, and the reaction is no longer self-heating. Stop agitation and separate the bottom aqueous waste from the top toluene phase. Charge water (175 kg) to the rich toluene phase and mix well to remove the phosphoric acid. Stop the agitation and separate the bottom aqueous waste from the product-rich toluene phase. Wash the toluene phase with 8 wt/wt % sodium bicarbonate solution (2 X 356 kg) to ensure that acid has been removed from the toluene phase (final pH 6.0). The concentration of the EDA solution in toluene was 0.214 g/mL (GC analysis), corresponding to 129.6 kg (90.9 M%) of EDA. The water content (KF) of the toluene phase was 0.16 %. Store the EDA-toluene solution protected from light at 5 ± 5 °C.

Acknowledgments

The authors would like to acknowledge the contributions of Dr. Chenkou Wei and Dr. Simon Leung for their efforts to study various aspects of this process using a React-IR. The authors would also like to thank the Chemical Development Operations department at the New Brunswick site of Bristol-Myers Squibb for their strong collaboration in the successful preparation of three pilot scale batches.

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20. Ethers have been used to prepare EDA
21. Solubility of the toluene solution in water is 0.067 wt/wt% at 24 /C.
22. Aldrich compound.

Chapter 10

Synthesis and Processing of Energetic Materials – Considerations for Safe Scale-up of Potentially Hazardous Reactions

Nicholas A. Straessler, Louis F. Cannizzo, and Michael W. Lesley[*]

Research and Development, ATK Aerospace Group, Brigham City,
Utah 84302, United States
[*]E-mail: Michael.Lesley@ATK.com

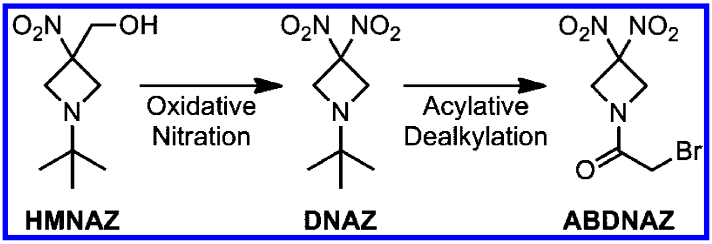
The synthesis and handling of energetic materials requires several cautionary practices beyond what is normally expected for non-energetic compound processes. We describe herein the additional items that are taken into account as the synthesis and development of an energetic material progress. Topics addressed include what is an energetic material, sensitivity and stability measurements, synthetic design for safety, energy content determination and control methods, transportation, and waste disposal. Emphasis is placed on the use of differential scanning calorimetry, reaction calorimetry, and accelerating rate calorimetry to characterize the energetic-related hazards of a reaction and its products. The synthesis of 1-bromoacetyl-3,3-dinitroazetidine, a clinical anti-cancer candidate derived from the explosive 1,3,3-trinitroazetidine, is used as a model process for demonstrating some of the techniques described here.

Introduction

Synthetic chemistry involves an intrinsic element of risk that generally increases with the scale of the reaction. Contributors may include applied heating, exothermic reactions, flammable solvents, and toxic or hazardous materials. Scale-up of processes containing these items can be a recipe for disaster if careful engineering and control are not practiced. The potential hazards of a reaction increase further when preparing energetic materials,

In Managing Hazardous Reactions and Compounds in Process Chemistry; Pesti, et al.;

where the consequences of an undesired thermal runaway are magnified by the increased energy content of the materials. Energetic materials classified as explosives are critical to the defense, propulsion, and mining industries but often are not considered for other applications due to their inherent dangers. Those not falling into explosives classifications are often still sufficiently energetic to pose appreciable safety concerns and, as a consequence, are usually not investigated. In 2012 we reported (*1*, *2*) the synthesis (Scheme 1) of a novel anti-cancer candidate, 1-bromoacetyl-3,3-dinitroazetidine (ABDNAZ) from 1-*t*-butyl-3-hydroxymethyl-3-nitroazetidine (HMNAZ). ABDNAZ successfully completed Phase 1 clinical trials with very encouraging results which has led to further clinical development and the initiation of Phase 2 clinical trials slated for 2014 (*3*).



Scheme 1. Two-step synthesis of ABDNAZ.

ABDNAZ is a derivative of the high-explosive 1,3,3-trinitroazetidine (TNAZ). The similarities to TNAZ (*4*), namely the geminal-dinitro moiety attached to a geometrically strained N-heterocycle, warranted thorough investigation of the energetic material-related hazardous properties of ABDNAZ (Figure 1).

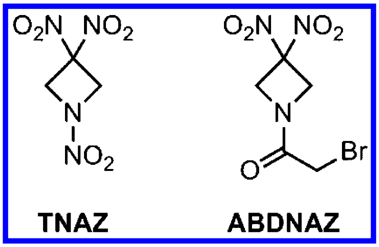


Figure 1. TNAZ and ABDNAZ.

Ultimately, it was concluded that ABDNAZ does not meet any explosive classification, but contains enough stored chemical energy to be considered an energetic material and warrant extra care in handling. However, the identified hazards do not preclude processing of the material, and the potential therapeutic advantages of ABDNAZ (*5*, *6*) far outweigh its manufacturing risks, providing proper production safeguards are employed. The development and efficacy of ABDNAZ is an excellent example of a compound that successfully transcends fields (defense to pharmaceuticals), and also demonstrates the merit of cross-discipline research using a largely untapped category of materials.

Nitroglycerine (NG), a well-known vasodilator used to treat heart conditions, is similar to ABDNAZ in that it is an energetic material with pharmaceutical applications. However, NG fits the definition of a true explosive and therefore processing it differs from ABDNAZ.

It is our intent here to provide a guide for the research and development of materials that are defined as energetic but not classified as explosives. The goal is to encourage and facilitate safe cross-discipline investigation of compounds that may otherwise be avoided because of their perceived risks. We focus on utilizing techniques and instruments that are available to many chemical manufacturing organizations and research institutions. Using our experience and data from the synthesis of ABDNAZ, we demonstrate how differential scanning calorimetry (DSC), reaction calorimetry, and accelerating rate calorimetry (ARC) can be employed to develop safe procedures for energetic processes and materials. Some general comments on synthesizing and handling energetic materials using examples that are not directly related to ABDNAZ are also provided.

Discussion

General Commentary on Energetic Materials

Energetic materials contain significant quantities of stored chemical energy (i.e., high positive heat of formation) and can have the potential to undergo rapid exothermic decomposition. For the subset of energetic materials classified as explosives, common compound types are strained nitrogen heterocycles, nitrogen rich materials, or ones that contain at least one of the following functional groups (*7*):

- nitro ($-NO_2$)
- nitrate ester ($-ONO_2$)
- nitramine ($-NNO_2$)
- diazo ($-N_2$)
- azide ($-N_3$)

Compounds consisting of a high percent composition of these functional groups should be evaluated for their energetic properties. The bulk of the literature on energetic materials discusses them in the context of explosives or propellants. However, an important distinction to be made is that a compound may be energetic but not explosive. All explosive compounds are energetic materials, but all energetic materials are not explosives. Explosives are metastable compounds that upon initiation will undergo deflagration or detonation; or transition from the former to the latter (*8*). A key feature in defining an energetic material as an explosive is not the energy yield upon decomposition, but rather the rate of the decomposition (i.e., the generation of heat and gas) (*9*). A molecule's 'oxygen balance' is a measure of its weight percent oxygen (*8*). Compounds with a positive oxygen balance contain a sufficient amount of oxygen to fully oxidize all other atoms in the molecule (e.g., C→CO_2, H→H_2O, etc.). Generally speaking, a higher oxygen balance indicates a stronger propensity for detonation, while compounds with a lower (negative) oxygen balance are less likely to detonate. Explosives testing, categorization, and safety have been thoroughly described elsewhere (*10–12*).

Energy Content and Thermal Stability Determination by DSC and ARC

Complete characterization of energetic materials involves a range of analyses including chemical composition, thermal properties, and response to various applied stimuli (*10*). The array of analytical tools that make up these tests is usually not available to most chemical institutions, so a rapid first-pass analysis using common instrumentation is preferred. For this purpose, DSC is optimal. DSC provides a quick and quantitative experimental indication of the magnitude of the exotherm given off by a material at its decomposition temperature. The DSC decomposition onset temperatures are ‘extrapolated onset’ temperatures (i.e., the intersections of a line drawn tangent to the steepest slope of the peak with the baseline). A DSC report gives the exotherm in terms of energy released per mass-unit of the subject material, typically in J/g. This energy is the negative of the enthalpy change upon decomposition. To get an accurate estimate of the energy, hermetic DSC capsules, which confine the products of the reaction, must be used. The lightweight aluminum capsules supplied by many instrument vendors tend to leak, and consequently erroneously low heat of reaction values may be obtained.

Table I displays the DSC heat of decomposition values (*13*) of some common explosives and ABDNAZ (*1*). From this data set, it is clear that ABDNAZ has a decomposition energy that is typical of explosives, although it cannot be classified as an explosive on this basis alone.

Table I. DSC decomposition onset temperatures and approximate exotherm magnitudes of some common explosives and ABDNAZ.

Material	*DSC Onset Temperature (°C)*[a]	*Magnitude (J/g)*
TNT	334	3700
NG	190	4300
RDX	222	4400
HMX	284	3800
PETN	198	3000
ABDNAZ	247	2400

[a] Ramp rate = 20 °C/min.

As a general guideline, compounds that exhibit decomposition energies ≥400 J/g have a significant probability of being explosives, or exhibiting undue thermal runaway hazards. This is supported by Tuma and Bagner (*14*) who suggest that drop weight tests (an indicator of impact sensitivity) and subsequent detonation velocity tests are necessary for samples with decomposition energies greater than 100 cal/g (418 J/g). A more recent monograph by Stoessel (*15*), in a discussion of the severity of runaway reactions, proposes that reaction mixtures with decomposition energies of 400-800 J/g be classified as potentially high severity (sharply increasing temperature vs time) thermal runaway risks. Presumably this would apply to the individual energetic reaction products as well.

The temperature of the decomposition onset can also be used as a preliminary safety indicator. Many compounds with onset of decomposition values as low as 150 °C have been handled safely in our laboratories. It must be emphasized that, before handling or storing such materials in large, production-scale quantities, they should be characterized with a method that is more sensitive than DSC to bulk self-heating effects.

In our laboratory, we use ARC (*16*) and an internally developed ‘simulated bulk autoignition’ test (SBAT) (*17*) for bulk thermal stability analysis (*18*). With solid, non-volatile energetic materials, our experience is that the initial SBAT exotherm temperature is approximately the same as the initial ARC exotherm temperature in a step-heat experiment conducted at a thermal inertia (phi) factor (*16*) of approximately two. Thermal inertia (phi) is an indicator of the sensitivity of an ARC measurement. It is a measure of the fraction of the heat of reaction that goes into heating the reaction vessel instead of the subject material. For a massless ARC sample container (ultimate sensitivity) the phi factor is equal to one.

As implied above, if a material gives off ≥400 J/g in the DSC analysis, it is advisable to evaluate its response to impact, friction, and electrostatic discharge (ESD). These tests, described in the literature (*10*), will need to be conducted by an organization with expertise in explosives processing as erroneous results may be obtained by inexperienced researchers. If the material is insensitive to these stimuli, then reaction calorimetry and ARC (or other bulk thermal stability analysis such as SBAT) should also be performed (described later) to verify safety. If the material gives an energetic response (i.e., it is “sensitive”) to the mechanical and ESD tests, then an experienced explosives expert should be consulted to perform additional analysis (*10*) to determine if the material is a true explosive. Subsequent processing of the explosive should be handled only by someone experienced in the field. An energetic material that is not an explosive can be safely processed with the appropriate precautions by someone who is not an explosives expert.

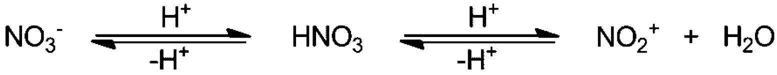
Desensitization for Safety

A desensitizing liquid may be used to reduce the likelihood of stimuli-induced decomposition of an energetic material. This can enhance safety while storing or transporting the material. The function of the desensitizing liquid is to absorb and dissipate heat generated upon impact or friction, thereby inhibiting the propagation of the thermal decomposition process from one molecule to another. A material can be desensitized by treating it with an unreactive liquid (~15 wt%) that can later be removed by evaporation if necessary. Water, alcohols, chloroform, methylene chloride, and liquid alkanes are frequently used. If the energetic material is a solid, it should have minimal solubility in the desensitizing liquid. In contrast, a desensitizing liquid should be chosen such that it completely dissolves a liquid energetic material.

For solid materials that respond unfavorably to mechanical or electrical stimuli, changing the crystal density and morphology may render them less sensitive. Generally, amorphous powders and low density materials tend to be less sensitive than highly crystalline and high density materials. Density and morphology changes are most safely accomplished by solution or slurry techniques (e.g., manipulation of precipitation methods). Grinding, milling, and other solid-state processing of energetic materials should be avoided until the properties of the material are fully understood. If an energetic material must be subjected to a friction-generating process, it should be carried out as a slurry in a solvent that has proven to desensitize that specific material.

Nitrations

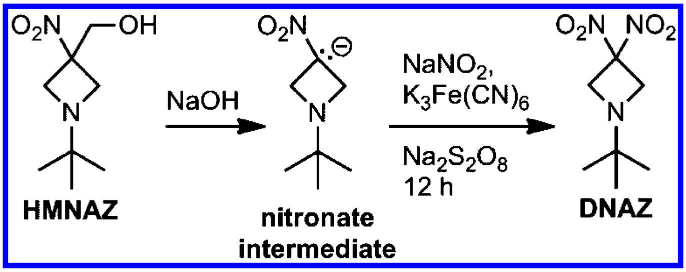
The most common energetic moiety is the nitro group; hence nitration reactions are prominent in the synthesis of energetic materials (*7*). Typical nitrating reagents such as mixed acids or nitric acid are harsh, corrosive and can evolve large amounts of NO_X gases, especially if heated during reaction. It is wise to select the mildest nitrating reagent available that will accomplish the desired transformation with minimal decomposition of starting materials and products; not only for the sake of yield but because decomposition of energetic materials can be autocatalytic and result in violent fuming (*19–21*). A general overview of safe nitration practices on an industrial scale is available in the literature (*22*) . In mixed acid nitrations, nitric acid is combined with concentrated sulfuric acid (i.e., ~95%) to form the nitronium cation (NO_2^+) which adds to an electron rich molecule by way of electrophilic substitution. The reaction can be effective using nitric acid in a range of concentrations. To increase safety, an inorganic nitrate salt can be used in place of nitric acid. The resulting initial equilibrium between the nitrate salt and nitric acid limits the amount of nitric acid and subsequent nitronium ions available in solution to react (Figure 2) (*23*).



$$NO_3^- \underset{-H^+}{\overset{H^+}{\rightleftharpoons}} HNO_3 \underset{-H^+}{\overset{H^+}{\rightleftharpoons}} NO_2^+ + H_2O$$

Figure 2. Solution equilibria resulting from the combination of a strong acid (e.g., sulfuric acid) with a nitrate (NO_3^-) salt to form nitric acid (HNO_3) and nitronium cation (NO_2^+).

Another mild nitrating method is oxidative nitration used to create geminal-dinitro species such as 1-*t*-butyl-3,3-dinitroazetidine (DNAZ) (Scheme 2). This reaction is performed in aqueous media with or without an organic co-solvent, and is effective for nitrating nitro compounds with a range of functional groups (*24*). The advantage of oxidative nitration is that NO_2 adds to the substrate via the nitrite anion as opposed to the nitronium cation as in mixed acid nitrations. The reaction is not dependent upon strong acids or their corresponding equilibria (protonation, dehydrogenation), and can be controlled by the addition rate of the secondary oxidant. The limitation of oxidative nitration is that the substrate nitro compound must contain a leaving group (e.g., proton or hydroxymethyl) that permits the formation of a nitronate salt where a lone pair of electrons is localized on the carbon to be nitrated (Scheme 2).



Scheme 2. Conversion of HMNAZ to DNAZ via formation of a nitronate intermediate followed by aqueous oxidative nitration.

Other reagents have been developed to nitrate compounds that are susceptible to hydrolysis and oxidation under acidic conditions. Nitronium tetrafluoroborate and nitronium hexafluoroantimonate (Figure 3) are two examples of opportune salts capable of nitrating arenes, nitroarenes, arylcarboxylic acid esters and halides, and aryl nitriles (*25*). Both compounds are commercially available and indefinitely stable (*25*) at room temperature under anhydrous conditions. A multitude of nitrating methodologies along with the pros and cons of each has been reviewed by Olah et al. (*25*, *26*) and Albright et al. (*27*).

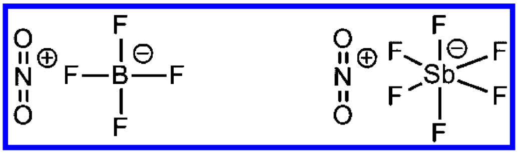
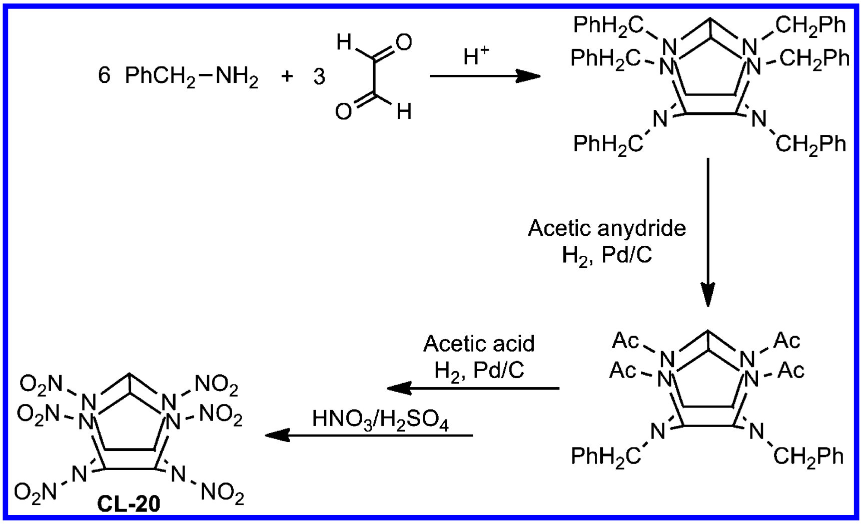


Figure 3. Nitrating agents nitronium tetrafluoroborate (left) and nitronium hexafluoroantimonate (right).

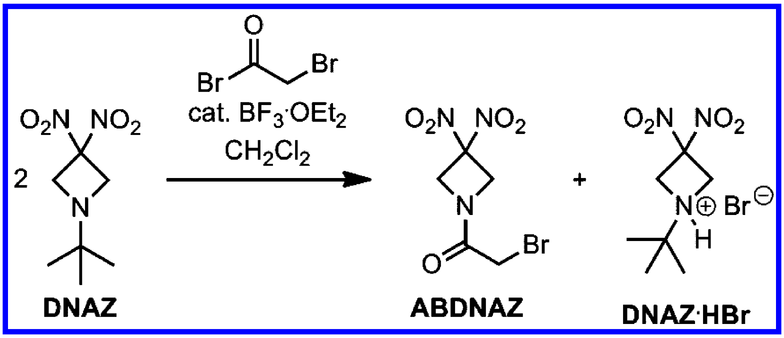
Synthetic Design for Safety

The synthesis of an energetic material should be designed such that the energetic moiety is added as late in the sequence as possible. This makes it safer to process and store intermediates. An outstanding example of late-stage nitration is the synthesis of hexanitrohexaazaisowurtzitane (CL-20), an extremely powerful hexa-nitramine explosive (Scheme 3) (*28*). CL-20 is prepared starting with the condensation of glyoxal with benzylamine, followed by reductive debenzylation/acetylation, and concluding with nitration of all the secondary amines (*29*, *30*). Nitration at only the very end minimizes the hazards of synthesizing CL-20 by allowing the majority of the processing to take place with non-energetic (i.e., non-nitro) molecules.



Scheme 3. Synthesis of CL-20 from benzylamine and glyoxal. Note the addition of six nitro groups as the last step.

Another safety mitigation is to separate energetic materials by dissolution rather than by filtration. For example, in the preparation of ABDNAZ, DNAZ·HBr precipitates from the acylative dealkylation solution during the reaction (Scheme 4).



Scheme 4. Conversion of DNAZ to ABDNAZ and DNAZ·HBr. ABDNAZ is formed in solution while DNAZ·HBr precipitates as a solid. The solid is separated from ABDNAZ by dissolution in water to minimize handling hazards.

In early developmental stages, DNAZ·HBr was removed by filtration. However, friction and impact testing showed it is sensitive to mechanical stimuli with exothermic decomposition energy of 2100-2300 J/g at 177 °C (onset) as determined by DSC. We solved this potential hazard by dissolving the solid with water to eliminate handling it in its sensitive state. Salts of energetic materials tend to be more sensitive than their covalent analogs; this is particularly evident with picrate and styphnate salts (*8*). Although, it is relevant to point out that sensitivities of energetic salts can vary with the molar mass of the counterion which ultimately affects the molecule's molar volume, density, and the number of intermolecular hydrogen bonding contacts (*31*). For example, Fischer et al. report that the hydrochloride salt of imidazole-1-sulfonyl azide is sensitive to impact while the hydrogen sulfate salt is not (Figure 4) (*31*).

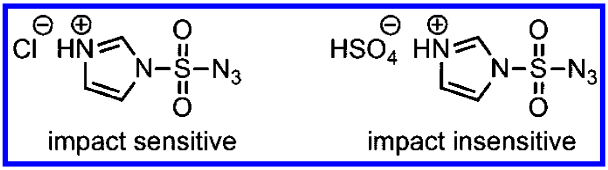


Figure 4. The molecular structure of imidazole-1-sulfonyl azide hydrochloride (left) and imidazole-1-sulfonyl azide hydrogen sulfate (right). The size of the anion affects the molecule's sensitivity to impact (31).

Perhaps the most important approach to investigating energetic materials is to start small by using micro-scale chemistry techniques. Initial synthesis reactions, particularly for new materials, should be run at milligram scales. There is no universal value in terms of mass that is both sufficient for characterization and definitively safe to handle. Small quantities will limit the potential damage and injury that could occur via spontaneous decomposition of the material, or eruptions caused by uncontrollable reaction exotherms. Moreover, small-scale reactions allow for semi-quantitative evaluation of the reaction thermodynamics by simply monitoring the temperature change during the process. The first synthesis of a new compound should be carried out to produce only enough material to get preliminary room temperature chemical analysis and then DSC data.

Note that even routine chemical analysis can be hazardous if the decomposition products of a compound are highly thermodynamically favored (*32*). If a compound is too unstable to obtain room temperature chemical characterization, further development is not recommended except possibly for the purposes of fundamental discovery but with extreme caution. Once it is confirmed that the isolated products or product mixtures are stable by DSC analysis at ambient conditions, then incrementally larger quantities should be prepared as needed for mechanical and ESD stability testing. High temperature chemical analysis such as gas chromatography should be avoided until the compound's decomposition temperature is determined by DSC.

Safety Equipment

Plastic shielding should always be employed when synthesizing new energetic materials (to contain any glass fragments produced by the potential rapid decomposition of the reaction mixture) until their thermal stability and sensitivity are determined, and the reaction thermodynamics are established. Shielding is also imperative when concentrating a solution of an explosive such as on a rotary evaporator or even just in a fume hood. In addition, standard personal protective equipment including safety goggles, flame retardant lab coat, and chemical resistant heavy duty gloves are necessary. To be safer, a full face shield, a leather or rubber apron, and neck/throat protection could be worn.

When dealing with reactions that have the potential to thermally run away, copious amounts of ice should be on-hand for rapid quenching during the incipient stages of a possible uncontrollable situation. If reagents or solvents are too reactive with water, sand may be used in place of ice. Teflon sleeves, tape, gaskets, and O-rings should be used on all energetic material processing equipment to avoid glass-to-glass and metal-to-metal contact. Precautions should be taken to seal off any areas that pose potential "pinch points" where energetic material could get trapped and exposed to friction. Fritted glass filters should also be avoided. Energetic materials should never be transferred or manipulated with metal devices (spatulas, scoops, etc.); plastic or Teflon tools should be used instead. Similarly, plastic, electrostatic dissipative or conductive containers (e.g., Velostat) are preferred over glass for storage of energetic materials.

Transportation and Waste Disposal

If energetic material is going to be shipped, a competent authority recognized by the producer's country must be engaged to determine the appropriate shipping classification for the material (*33*). In addition, explosive-related materials usually require shipment in an inerted (e.g., dissolved or wetted) state. The synthesis of energetic materials frequently results in a waste stream that also contains energetic materials. Similar to the desired isolated reaction product, waste streams (solids and liquids) should also be assessed for energy of decomposition, stability, and sensitivity. In the case of ABDNAZ, the co-product (DNAZ·HBr) of the reaction is more sensitive than the targeted product. Energetic material waste streams that display sensitivity, especially solids, should be desensitized as a soon as possible after their generation, and their storage time should be minimized. Typically, waste will be shipped to an approved chemical waste treatment facility or incinerator. The treatment facility should be notified ahead of time of the exact contents, and have agreed to accept the waste. Depending on the capabilities of the originating facility, aqueous waste streams may be amenable to on-site processing in a bio-reactor. Several such systems have been designed specifically to digest propellant waste streams containing perchlorates (*34*, *35*). In many cases, nitrates can be consumed by the same systems and are often preferred by the bacterial cultures. Following an initial base hydrolysis, nitramines can also be treated in these bio-reactors. Local experts should be consulted to verify the capability of a bio-reactor prior to introducing any new waste stream.

Controlling Exothermic Reactions

This section addresses the theory used to determine if an exothermic chemical reaction is safe to carry out in a particular reaction vessel equipped with its own cooling mechanism. The application and associated calculations with examples are provided elsewhere (*14*, *15*, *36*, *37*).

When scaling up any exothermic reaction beyond lab-scale, it is first essential to determine the total heat that could be produced by the reaction mixture. This can be obtained from reaction calorimetry, or in some cases from careful DSC experiments. ARC on a reaction mixture can sometimes be used to simulate the course of a possible thermal runaway and determine the heat of reaction as well. DSC has the drawback that reactants cannot be added while the experiment is in progress, and most ARC models do not permit this either. In a reaction calorimeter, the heat flow response can be measured immediately after a reactant is added.

If DSC is used, it is essential that the capsule not leak and that a large enough sample is used so that volatile components do not simply evaporate into the headspace of the capsule. The DSC capsules should be weighed before and after the experiment to verify that no leakage has occurred. Of course, one also has to be careful that the sample size is not so large that it will burst the capsule.

The enthalpy of reaction ΔH_r (negative of the exothermic heat of reaction reported in a calorimetric experiment) is used to calculate an adiabatic temperature rise ΔT_{ad} :

$$\Delta T_{ad} = \frac{-\Delta H_r}{C_p} \tag{1}$$

where ΔT_{ad} is the adiabatic temperature rise in °C, ΔH_r is the enthalpy of the reaction in joules per gram of reactor contents, and C_p is the specific heat capacity (J/g °C) of the reaction mixture. This equation is obtained by a simple energy balance.

The adiabatic temperature rise allows one to estimate the maximum temperature rise if the reaction gets out of control and releases all of its energy with theoretically no dissipation to the surroundings. Questions that should be addressed are:

- Is the heat of reaction high enough to cause boiling of the reactor contents? If not, the thermal hazard from the reaction is probably minimal.

- Can the heat of reaction heat the reactor contents to a temperature where a side reaction (e.g., hazardous decomposition of the intended reaction product or decomposition of a by-product) could be triggered?

If the thermodynamics indicate that the reaction has enough energy to create a hazardous situation under adiabatic conditions, then one must consider how the heat removal capacity of the reaction vessel compares to the rate of heat generation by the chemical reaction. It must be established that the vessel can remove the heat of reaction as it is generated and prevent a hazardous thermal runaway (*36*).

The first step is to measure the maximum heat flow from the synthesis reaction in the temperature range where it is being conducted. Reaction calorimetry is a convenient method for doing this. For non-autocatalytic reactions run under isothermal conditions, the initial rate is the maximum rate. Then, as the reactants are depleted, the rate declines. For autocatalytic reactions, the rate initially increases with time as the catalytic reaction product is formed until a maximum is reached and then the rate declines as the reactants are consumed. The peak in the autocatalytic rate curve is used as the maximum rate.

Next, the maximum heat flow must be compared with the heat removal capacity of the reactor. If the heat transfer coefficient of the equipment is known, this can be calculated. For a vessel with unknown heat transfer characteristics, the reactor can be filled with water (or the reaction solvent), heated to elevated temperature with stirring, and then the cooling liquid valve fully opened. The temperature of the reactor contents is measured versus time, and from this the heat transfer coefficient (and heat removal rates) can be determined. If the maximum heat flow is considerably less than the heat removal capacity, then it is possible to keep the reaction under control with the process equipment. However, malfunctions in the cooling equipment still ought to be considered as a potential hazard and contingencies considered for unexpected situations.

If the maximum heat generation rate and the heat removal rates are similar, a mathematical reactor model, based on both kinetics and heat transfer, can be used to help decide if the reaction can be scaled-up in the proposed equipment (*36*, *37*). This will predict the course of a possible thermal runaway and further help define safe operating temperature ranges for the process. These models account for decreases in reaction rate that occur as reactants are consumed, and they are more realistic than simply comparing the maximum rate of heat production with the rate of cooling.

These calculations can aid in the decision to scale-up a reaction but are only part of the overall risk assessment. Other factors including bench-scale experience and a fundamental chemical understanding of all the reactants and reagents, and their corresponding hazards need also to be factored into the assessment. Appropriate shielding and remote controls should be employed for all large-scale reactions, energetic or not.

Reaction Calorimetry – Synthesis of DNAZ

In this section, the conversion of HMNAZ to DNAZ (Scheme 2) is used as an example of how reaction calorimetry can be employed to quantify the heat given off by an exothermic reaction. Conversion of DNAZ to ABDNAZ was shown to be endothermic by reaction calorimetry and is therefore not discussed in detail here. The repeatable mass balance and high yield of ABDNAZ along with accurate byproduct characterization signified the absence of any undesired side reactions. However, careful characterization of the reaction mixture did indicate that the hydrolysis of bromoacetyl bromide to bromoacetic acid will occur slowly.

The synthesis of DNAZ was studied in a stirred reaction calorimeter to obtain quantifiable heat flow data to assess the magnitude of the exotherms. Table II shows the steps that were performed to represent the full-scale synthesis of DNAZ. Figure 5 shows the reaction calorimeter heat flow curve for the first 4 h of total elapsed reaction time (Figure 7 shows a continuation of the heat flow curve to 25 h total elapsed reaction time).

Formation of a nitronate salt by addition of HMNAZ to aqueous NaOH (Table II, Step 3) produced a very small exothermic enthalpy of solution, -11.1 kJ/kg of HMNAZ, calculated from the area under the curve in reaction calorimetry. The exothermic enthalpy change observed by the addition of the oxidation mixture ($NaNO_2$ and $K_3Fe(CN)_6$) to the nitronate solution (Table II, Step 5) was also small, -3.57 kJ/kg of reactor contents. In this case, 'reactor contents' is the mass of everything in the reactor after the addition step in question.

Beginning with the addition of $Na_2S_2O_8$ to the reaction mixture held at 10 °C (Table II, Step 6) the maximum exothermic heat flow for the synthesis is about 45 W/kg of reactor contents, and it declines below 15 W/kg of reactor contents after 40 min (~0.6 h after $Na_2S_2O_8$, or ~2.4 h total elapsed reaction time) (Figure 6). The heat flow (in W/kg) is the instantaneous heat generation rate from the reaction; the enthalpy change (in kJ/kg) is the total integrated heat produced by a thermal event.

The total exothermic enthalpy change of this reaction over the 40 min period is only -50.38 kJ/kg of reactor contents (obtained by integration of the curve). In the event of a total cooling failure, and if the system were adiabatic, this amount of energy would only be enough to raise the temperature of the system by 12.0 °C (using eq 1) assuming that the reactor contents have the heat capacity of water (4.184 kJ/kg °C). Still, it is important to verify that a reaction vessel has enough heat transfer capability to remove this amount of heat flow so the temperature can be kept constant.

Table II. Synthesis of DNAZ for reaction calorimetry study.

Step	*Description*
1	Add H_2O (68 mL) to the reactor and allow to equilibrate at 25 °C.
2	Add NaOH (1.93 g) and allow to dissolve.
3	Add HNMAZ (4.53 g) and allow to dissolve via formation of the nitronate salt.
4	Cool the reactor contents to 10 °C.
5	Add a solution containing $K_3Fe(CN)_6$ (0.79 g), $NaNO_2$ (6.64 g), and H_2O (18 mL).
6	Add $Na_2S_2O_8$ (8.15 g) and allow to react for approximately 40 minutes at 10 °C.
7	Heat the reactor to 25 °C and stir for ~23 h.

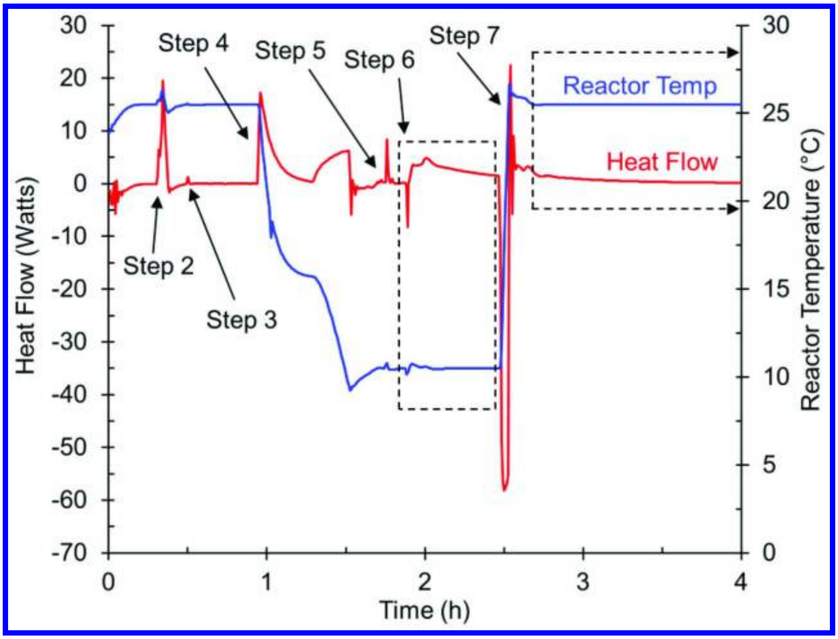


Figure 5. Reaction calorimeter heat flow curve (in watts) for the entire synthesis of DNAZ. Refer to Table II for description of the indicated steps. Dotted lines indicate the portions of the heat flow curve that are expanded in Figures 6 and 7 (Figure 7 shows a continuation of the curve to 25 h). Reproduced with permission from reference (1). Copyright 2012 American Chemical Society.

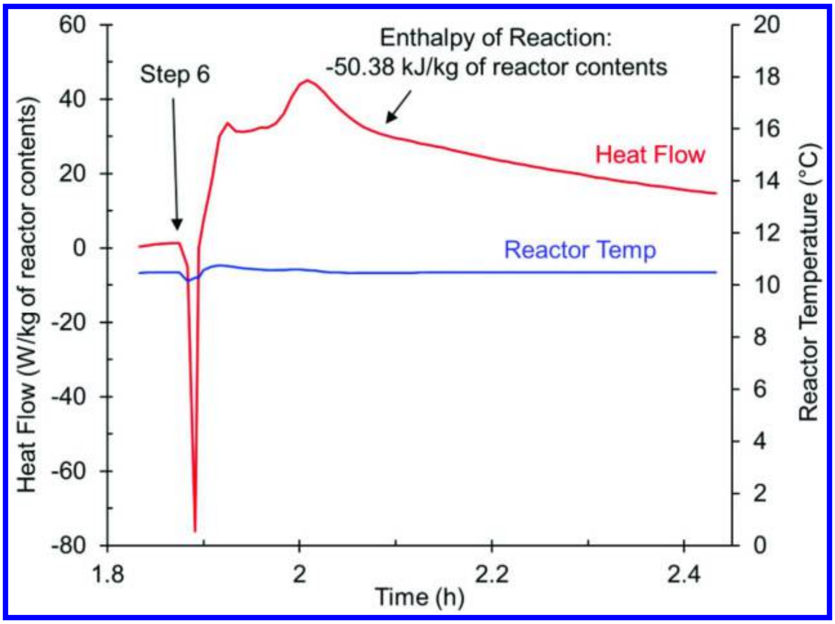


Figure 6. Reaction calorimeter heat flow curve (in W/kg of reactor contents) for the synthesis of DNAZ following addition of secondary oxidant, $Na_2S_2O_8$ (Table II, Step 6). Reproduced with permission from reference (1). Copyright 2012 American Chemical Society.

Once the heat flow decreased to less than 15 W/kg of reactor contents (shown in Figure 6), the reaction was heated to 25 °C (Table II, Step 7). Figure 7 shows the heat flow curve after heating the reaction mixture to 25 °C (total elapsed reaction time range shown in Figure 7 is ~2.5 h to 25 h). A small number of data points (about 10 min worth) are lost during heating and equilibration of the calorimeter at 25 °C. After heating to 25 °C the maximum exothermic heat flow is on the order of 30-35 W/kg of reactor contents, and it declines to zero after 2.7 h at 25 °C (at ~5.3 h total elapsed reaction time). The total integrated enthalpy of reaction for the 2.7 h period is only -40.15 kJ/kg of reactor contents. Therefore, a thermal runaway is impossible under these conditions, as the additional adiabatic temperature rise would be <10 °C.

While the reaction calorimetry suggests conversion of HMNAZ to DNAZ is complete 2.7 h after the reaction is heated to 25 °C following the addition of $Na_2S_2O_8$, the reaction was stirred for up to 72 h to assess the stability of the mixture under these conditions. Studies showed that there was no adverse effect of time as reactions ranging from 12-72 h provided essentially identical purities and yields of DNAZ which separates from the reaction mixture as a viscous yellow/orange liquid. The product is separated by extraction with CH_2Cl_2 and never isolated neat due to previously reported (*4*) thermal hazards and our own DSC and ARC data.

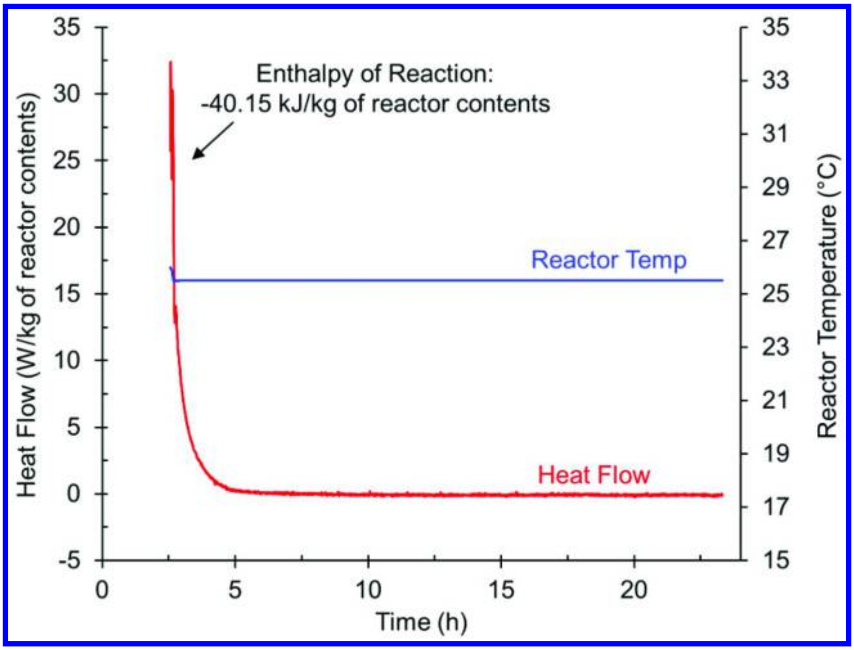


Figure 7. Reaction calorimeter heat flow curve (in W/kg of reactor contents) for the synthesis of DNAZ after heating from 10 °C to 25 °C (Table II, Step 7). Reproduced with permission from reference (1). Copyright 2012 American Chemical Society.

Differential Scanning Calorimetry

Differential scanning calorimetry analysis was conducted on all four of the starting materials and products involved in the two-step conversion of HMNAZ to ABDNAZ to determine their respective thermal stability. Samples were analyzed at a heating ramp rate of 20 °C/min in aluminum pans (*38*). Lower heating ramp rates can provide more precise onset values. By our own DSC threshold value (400 J/g), HMNAZ, DNAZ, DNAZ·HBr, and ABDNAZ qualify as energetic materials (Table III); though HMNAZ contains notably less energy than the other three compounds. The low decomposition onset temperature (135 °C) displayed by DNAZ combined with the prior report (*4*) of its low thermal decomposition was sufficiently concerning to prohibit isolation of this compound neat. HMNAZ, DNAZ·HBr, and ABDNAZ were subjected to impact, friction, and ESD testing. HMNAZ and ABDNAZ in their isolated forms were unresponsive to these stimuli, but DNAZ·HBr was sensitive to impact (*1*). Hence, the reaction procedures were modified as described earlier to dissolve DNAZ·HBr in water for separation rather than filtration.

Accelerating Rate Calorimetry

Accelerating rate calorimetry is a laboratory calorimetric method designed to simulate the adiabatic self-heating and thermal runaway behavior of bulk quantities of material (*16*). In adiabatic mode, the ARC calorimeter walls track the sample container temperature, resulting in a theoretically zero temperature gradient between sample and surroundings. This simulates the poor dissipation of heat in a large mass of decomposing energetic material. Temperature and pressure data are recorded during the experiment. Samples are heated stepwise in 5 °C increments, with adiabatic holds at each temperature. When the calorimeter detects an exotherm (defined as a self-heat rate in excess of 0.02 °C/min) it remains in adiabatic mode until the exotherm is finished or a preset upper temperature, pressure, or self-heat rate limit is reached.

Generally speaking, we avoid heating materials to temperatures within 50 °C of an initial ARC exotherm temperature (ARC experiment conducted at a phi factor on the order of two or lower) in short-term handling or processing. The step-heat ARC data are also an indication of longer-term storage stability, but the decision to store a material long-term in large quantities should be made on more than just an initial exotherm temperature. Isothermal aging experiments to detect destabilization of the material due to autocatalysis, the separation between the temperatures of thermal events in ARC and the storage temperature, and chemical understanding of the materials all come into play.

The four starting materials and products involved in the two-step conversion of HMNAZ to ABDNAZ were each analyzed by ARC to provide thermal safety information on handling them in larger quantities than bench-scale. Because DNAZ is stored in CH_2Cl_2 during the synthesis process, a sample of DNAZ in CH_2Cl_2 was also analyzed by ARC. With all materials except DNAZ·HBr, small (~0.3 g) samples were initially run in heavy 1in. diameter titanium bombs and allowed to self-heat to thermal runaway and/or autoignition. Then, runs with larger samples and/or smaller bombs (1/2in. diameter titanium or stainless steel) were made to increase the sensitivity of the measurements and provide a better representation of bulk thermal runaway behavior. To avoid bomb ruptures, the calorimeters were programmed to turn off before the samples autoignited, with the objective of only measuring the initial part of the exothermic thermal runaway. Phi factors, were on the order of 2-3 for the final, high sensitivity runs, except for DNAZ·HBr. DNAZ·HBr was only run at the 0.3 g sample size in a heavy bomb with a phi factor of about 10. All samples were heated stepwise from 50 °C in 5 °C increments, while monitoring for exotherms at each hold temperature.

A summary of the ARC data for all samples can be seen in Table III. The temperature and pressure versus time, and self-heat rate versus temperature plots are available in the literature (*1*).

From these data, it was determined that the pure DNAZ was too unstable to store in large quantities. Storage under conditions of high dilution in methylene chloride helps to mitigate the thermal hazard, but we also determined that longer-term storage of this solution might pose a risk of gas evolution from decomposition in the storage drum. Lab-scale samples of DNAZ in methylene chloride have been stored at 25 °C for up to 30 days, and at 6-10 °C for up to a year without incident

(*1*). However, we prefer that the material be consumed as quickly as possible after making it. The other materials were deemed to be sufficiently stable to process and handle beyond the bench-scale.

Table III. DSC and ARC data for starting materials and products involved in the synthesis of ABDNAZ.[a]

Compound	*Lowest observed DSC exotherm onset temperature (°C)*[b]	*Magnitude of largest exotherm (J/g)*	*Lowest observed ARC exotherm temperature (°C)*
HMNAZ	209	785	115
DNAZ	135	2179	75
DNAZ in CH_2Cl_2	-	-	135
ABDNAZ	247	2429	125
DNAZ-HBr	177	2348	125

[a] Reproduced with permission from Reference (*1*). Copyright 2012 American Chemical Society. [b] Ramp rate = 20 °C/min

Conclusions

Compounds that contain multiple nitro groups or other high-energy moieties are generally avoided by industries other than defense, propulsion, and mining due to safety concerns. However, the success of energetic materials such as ABDNAZ that have crossed disciplines suggests that there is merit in broadening the investigation of these types of compounds for alternative applications. Many such compounds will likely fit the category of energetic but not explosive, and therefore can be safely processed by other industries employing a fundamental understanding of their properties and with appropriate safeguards.

Target molecules that are potentially energetic materials should initially be synthesized only in milligram quantities for chemical and thermal characterization, and then sensitivity testing. Plastic shields along with substantial personal protective equipment are recommended when synthesizing any new or uncharacterized energetic material. Only plastic or Teflon tools should be used to manipulate energetic materials. Processing equipment for energetic materials should be devoid of pinch points, metal-to-metal and glass-to-glass contact. As the scale of a reaction increases so should the degree of remote operation if possible. Any suspected energetic material, based on structure and chemical makeup, should be analyzed by DSC to experimentally quantify its decomposition energy. Compounds that yield over 400 J/g upon decomposition by DSC should be considered energetic and handled accordingly.

Impact, friction, and ESD testings should be performed on all energetic compounds to determine their sensitivity to mechanical and electrical stimuli. An explosives expert should be consulted for further, more specific, testing if a compound demonstrates high sensitivity. Sensitivity can be reduced by wetting or dissolving solid or liquid energetic materials respectively in an inert solvent. The sensitivity of solids can also vary with crystallinity, particle size, and morphology. ARC or other bulk thermal stability analysis should be used to determine the thermal safety issues involved in handling quantities of energetic materials larger than bench-scale. Energetic materials need to be classified and permitted by the appropriate governing authorities before being transported on public roads. Desensitization is recommended prior to transportation.

The preparation of an energetic material should be designed such that the energetic component is added as late in the synthesis sequence as possible to minimize the amount of time spent processing hazardous components. For exothermic reactions, it is necessary to verify that either: (a) the reactor contents can absorb the total heat of reaction without causing the reactor to boil over or triggering a dangerous decomposition; or (b) the cooling capacity of the reaction vessel is sufficient to remove the heat generated by the exotherm. These concepts apply to all scales that a reaction can be carried out.

ABDNAZ is an energetic material that has encountered remarkable success in clinical trials as an anti-cancer candidate. The development of ABDNAZ has been described here as an example of how to safely process an energetic material for non-conventional applications.

Experimental

Synthesis

ABDNAZ is prepared in two steps (Scheme 1):

1. Conversion of 1-*t*-butyl-3-hydroxymethyl-3-nitroazetidine (HMNAZ) to 1-*t*-butyl-3,3-dinitroazetidine (DNAZ) by aqueous oxidative nitration.
2. Catalyzed acylative dealkylation of DNAZ to ABDNAZ in methylene chloride.

Although both steps have been previously reported (*1*) we provide the detailed procedures here for the purpose of understanding the measurements involved to ensure reaction safety. The reaction sizes described below were used to make ABDNAZ for pre-clinical investigation. A contract research organization (CRO) used the same methods to produce kilo-quantities of ABDNAZ for clinical trials; batch size = 6 kg of DNAZ, average yield of ABDNAZ = 85%.

CAUTION: Our calorimetry and thermal data indicate that ABDNAZ is safe to handle as a dry solid under typical ambient processing conditions (i.e., 20-30 °C) and that DNAZ and DNAZ·HBr should be kept solvent wet or in solution. Nevertheless, *gem*-dinitroazetidines can undergo rapid decomposition and may be sensitive to impurities, heat, friction, impact, and electrostatic discharge. Handle with caution and appropriate safety equipment!

1-t-Butyl-3-hydroxymethyl-3-nitroazetidine (HMNAZ)

HMNAZ was obtained from Parish Chemical Company (Vineyard, UT) in ≥98% purity.

1-t-Butyl-3,3-dinitroazetidine (DNAZ)

A solution of sodium hydroxide (71.2 g, 1780 mmol) in distilled water (1470 mL) at 20-25 °C was treated with HMNAZ (97.6 g, 519 mmol) over 1 min. The mixture was stirred at ambient temperature for 1-2 h. The resulting nitronate solution was chilled to 10 °C and that was followed by the addition of a solution of potassium ferricyanide (17.2 g, 52 mmol) and sodium nitrite (143.2 g, 2075 mmol) in water (400 mL). Sodium persulfate (173.2 g, 727 mmol) was introduced at 10-15 °C over 2 min. The reaction temperature initially dropped and then increased by 10-15 °C. Once the exotherm began to subside, the reaction was warmed to 20-25 °C over 1 h and held for 12-16 h at that temperature. The resulting orange/brown emulsion was extracted with CH_2Cl_2 (3 x 450 mL). The combined yellow/orange organic extracts were dried (Na_2SO_4) and then concentrated with a rotary evaporator to ~450 mL. For quantification and identification purposes, a small sample of the solution was brought to dryness in vacuo yielding DNAZ as yellow/brown oil (CAUTION: solvent-free compound may undergo rapid energetic decomposition if sufficiently heated (*4*)). Yields were consistently >99% (*39*), spectral and analytical data matched those previously reported (*4*).

1-Bromoacetyl-3,3-dinitroazetidine (ABDNAZ)

Under a blanket of N_2, the CH_2Cl_2 solution of DNAZ (~1.15 M, described earlier) was treated with $BF_3 \cdot OEt_2$ (6.37 mL, 52 mmol) followed by bromoacetyl bromide (33.77 mL, 388 mmol). The N_2 purge was stopped, and the vessel was sealed with a rubber septum punctured with a stationary 20 gauge needle to serve as a pressure-release vent. The mixture was heated to a mild reflux and held for 6 h. Heating was stopped and CH_2Cl_2 (1000 mL) and distilled water (800 mL) were added in that order. The two-phase system was stirred vigorously for 16 h. The aqueous phase was removed and the organic layer washed with additional distilled water (4 x 500 mL). The organic solution was dried (Na_2SO_4) and concentrated on a rotary evaporator to approximately half its initial volume followed by addition of EtOH (250 mL). The remaining CH_2Cl_2 was removed at 25-30 °C causing a precipitate to form. The slurry was chilled in an ice bath for 30 min and the solid was collected by filtration, rinsed with cold EtOH (5 x 150 mL), and air dried to afford pure ABDNAZ (56.04 g, 81% yield (*40*)) as colorless crystals: mp 127-129 °C. IR (neat, cm^{-1}): 3013, 1677, 1586, 1567, 1446, 1368, 1338. ^1H NMR (400 MHz, acetone-d_6): 4.0 (s, 2H, $-CH_2Br$), 4.9 (br s, 2H, ring $-CH_2-$), 5.3 (br s, 2H, ring $-CH_2-$); ^{13}C NMR (acetone-d_6): 25.5, 58.5, 60.5, 107.6, 167.4. Anal. Calcd for $C_5H_6BrN_3O_5$: C, 22.41; H, 2.26; N, 15.68. Found: C, 22.52; H, 1.89; N, 15.60.

Flash Precipitation of ABDNAZ

A quantity of ABDNAZ was dissolved in EtOAc (mass of ABDNAZ in grams x 6 = mL of EtOAc). This solution was rapidly added to a beaker of stirred (500 rpm) heptane (mass of ABDNAZ in grams x 18 = mL of heptane) immediately resulting in a white precipitate. The suspension was stirred for 5 min and the solid was collected by vacuum filtration and rinsed with heptane. To ensure thorough solvent removal, air was pulled through the solid on the filter for 16 h. Analytical data matched that described previously for ABDNAZ.

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38. Heavy duty 15 μL (~200 mg) aluminum pans, Seiko A115-capsule, Perkin-Elmer part number N-5356003 with a truly hermetic cold-weld metal seal.

39. DNAZ was repeatedly recovered in near quantitative yields; stoichiometry of the ensuing reaction is based on quantitative conversion of HMNAZ to DNAZ.
40. Theoretical mol-ratio of DNAZ to ABDNAZ is 2:1. Yields of ABDNAZ are calculated using this ratio based on the starting amount of DNAZ.

Chapter 11

Addressing Process Safety Hazards: Replacement of para-Methoxybenzyl Chloride Leads to a Safer and Shorter Route

Oliver R. Thiel,* John R. Huckins, Derek B. Brown, Eric A. Bercot, John T. Colyer, Bobby Riahi, Rob R. Milburn, Steve M. Shaw, and Joe Tomaskevitch

Amgen, Chemical Process Research and Development, One Amgen Center Drive, Thousand Oaks, California 91320-1799, United States
***E-mail: othiel@amgen.com**

Access to kilogram amounts of 1*H*-benzimidazol-2-yl(4-hydroxyphenyl)methanone (**1**) was required in support of a development program. The initial synthesis used 4-methoxybenzyl chloride (PMBCl, **2**) as a reagent to set the protecting group, which required a careful hazard analysis prior to use in the first generation synthesis of **1**. The hazards associated with PMBCl made it a non-viable choice for long-term supplies, and therefore alternative chemistry was developed with a special emphasis on safety and efficiency. The final synthesis proceeds in two chemical steps with a high overall yield (80%) and the available data support the safety of the developed process.

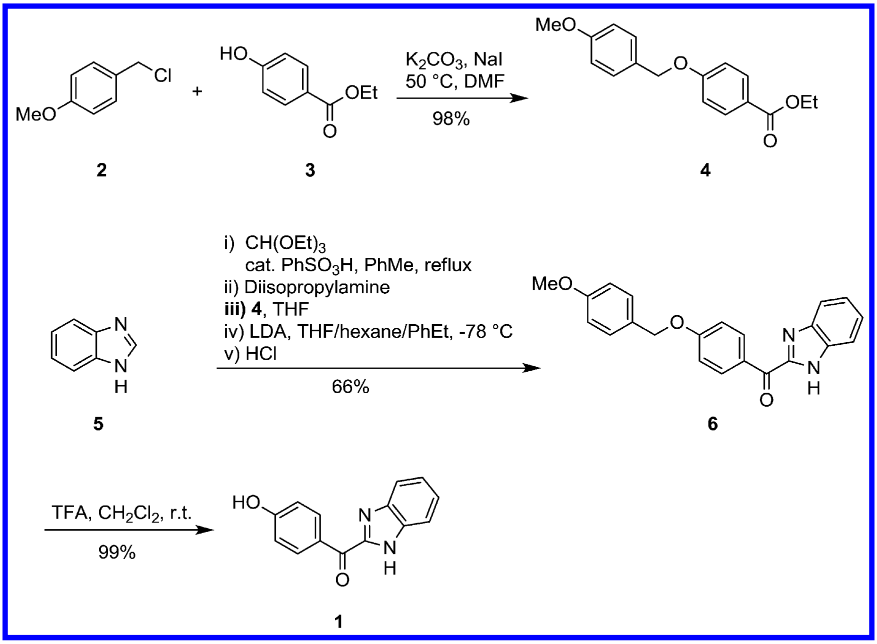
Introduction

A key priority for early phase process research and development is the delivery of kilogram amounts of drug substance under aggressive timelines. Depending on the molecular complexity of the target, the route used by the Medicinal Chemistry groups can serve as a ‘fit for purpose’ platform to enable early deliveries. Primary focus is then placed on addressing potential processing hazards, while ideally also simplifying workups and isolations. A process hazard analysis is routinely conducted and hazardous reaction steps or reagents are appropriately managed. Experience gained from the first delivery feeds into

In Managing Hazardous Reactions and Compounds in Process Chemistry; Pesti, et al.;

prioritization of next generation route selection efforts, in which hazardous reagents and steps are eliminated to the greatest extent possible.

Support of a recent development program at Amgen required access to kilogram amounts of 1*H*-benzimidazol-2-yl(4-hydroxyphenyl)methanone (**1**) as a key intermediate. The Medicinal Chemistry route to this building block relied on a three step sequence (Scheme 1). 4-Methoxybenzyl chloride (PMBCl, **2**) was employed to install a protecting group on ethyl 4-hydroxybenzoate (**3**) affording intermediate **4**. The key carbon-carbon bond formation was accomplished using transiently protected, and then deprotonated benzimidazole (**5**) (*1*). Towards this end benzimidazole was protected as the *N*-diethoxymethyl derivative using triethylorthoformate. Addition of electrophile **4**, followed by in situ deprotonation with lithium diisopropylamide (LDA) at low temperature and an aqueous acidic quench afforded intermediate **6**. The final deprotection of the 4-methoxybenzyl group was accomplished using trifluoroacetic acid in dichloromethane. Overall this efficient sequence provided the target intermediate in 65% yield (*2*).



*Scheme 1. Medicinal Chemistry route to key intermediate (**1**).*

Hazard Evaluation of 4-Methoxybenzylchloride and Screening of PMBCl Stabilizers

The 4-methoxybenzyl (PMB) group is a popular protecting group for alcohols and phenols due to its relative ease of installation and cleavage. It was chosen by our discovery colleagues over other alternatives since it could be easily cleaved under acidic conditions. The alternative use of a benzyl protecting group, followed by hydrogenative removal led to side reactions. The thermal hazards of PMB-Cl have been described in the literature (*3*, *4*), and recently a more detailed study was published (*5*). Several safety incidents involving inadequate handling or storage have been reported with this reagent, which are thought to be the result of an uncontrolled exothermic cationic polymerization with concomitant release of HCl gas. This knowledge led us to further evaluate the overall hazard potential of PMB-Cl prior to use on kilogram scale.

PMB-Cl decomposes in a runaway polymerization that is triggered by traces of HCl. The literature data suggests that unstabilized PMB-Cl can undergo autocatalytic decomposition within hours at temperatures of as low as 35 °C. Limited stability of at least 9 days at room temperature (25 °C) was achieved by storing PMB-Cl over solid potassium carbonate to scavenge trace acid (*5*).

Our own results corroborate and extend these findings. An interesting observation was made with regards to the effectiveness of stabilizers. Most commercial samples of PMB-Cl are stabilized with potassium carbonate. The efficiency of this heterogenous stabilizer is impacted by the minimal solubility and more efficient scavenging was observed in stirred systems (*5*). In our studies, exothermic decomposition and pressure build-up was detected at 66 °C using accelerating-rate-calorimetry (ARC) (Figure 1) (*6*). Conducting the ARC experiment using a stirred sample cell in the presence of additional spiked potassium carbonate did not increase the exotherm onset temperature. It was however noted that the time to maximum rate, defined as the time it takes for the decomposition reaction to reach its maximum rate from its onset temperature, could be delayed by having a reservoir of scavenging agent available (Table 1) (*7*). We noted significant differences in onset temperature and time to max rate depending upon the source of the PMB-Cl, suggesting that all lots should be examined upon receipt. The improved stability in stirred samples as compared to unstirred samples is a result which can be relatively easy rationalized for a heterogeneous scavenger due to mass-transfer limitations. While this finding is scientifically interesting, it has limited practical relevance, since storage of the material is usually performed without stirring.

Samples of material with the homogenous stabilizer amylene are also commercially available, and it was of interest to compare the efficiency of the stabilizers. Somewhat unexpectedly, amylene is not more efficient in delaying exothermic decomposition of PMB-Cl. Exothermic decomposition occurred as low as 56 °C (Figure 2, Table 1) (*8*). Similar to the previous trends, an extension in time to maximum rate could be achieved by simply adding larger amounts of the scavenger (Table 1). No conclusive recommendation can be made to which scavenger is preferred (homogenous or heterogeneous) based on these data. Ultimately neither scavenger led to a stabilization that would justify the safe usage of PMB-Cl on very large scale.

Together with the previously published results (*5*), we concluded that PMB-Cl could be used on limited scale with the following precautions:

- purchase of fresh reagent as needed in limited quantities
- testing of each batch for thermal stability
- use of a stabilizer to minimize potential of exothermic decomposition
- cold storage of reagent (2–8 °C)

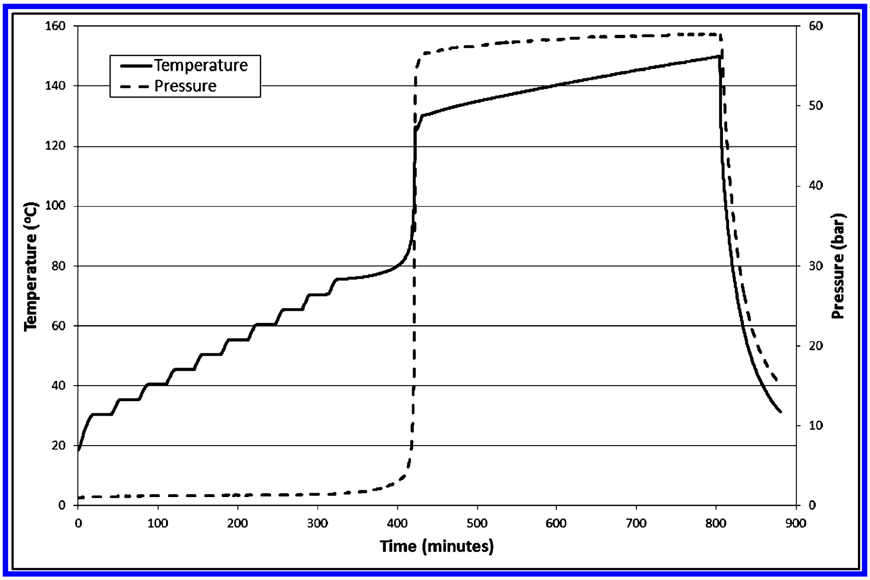


Figure 1. ARC-trace of PMB-Cl stabilized with potassium carbonate.

Table 1. Summary of ARC results for commercial PMB-Cl samples.

Sample	*Stirring*	*Additive*	*Onset T (°C)*	*Time to max rate (min)*[c]	*Max T rate (°C/min)*	*Max P rate (bar/min)*	*Energy (J/g)*
1[a]	-	-	76	47	29	65.5	221
1[a]	+	3.4 wt% K_2CO_3	71	66	24	46.6	234
1[a]	+	10 wt% K_2CO_3	66	137	14	28.8	246
2[b]	-	-	66	67	20	28.9	247
2[b]	-	0.57 wt% amylene	71	55	20	29.9	237
2[b]	-	5.8 wt% amylene	56	142	8	12.4	273

[a] Supplier A, stabilized with solid potassium carbonate. [b] Supplier B, stabilized with amylene. [c] Indicates the time it takes for the sample to reach its maximum temperature rate under adiabatic conditions starting from the onset temperature.

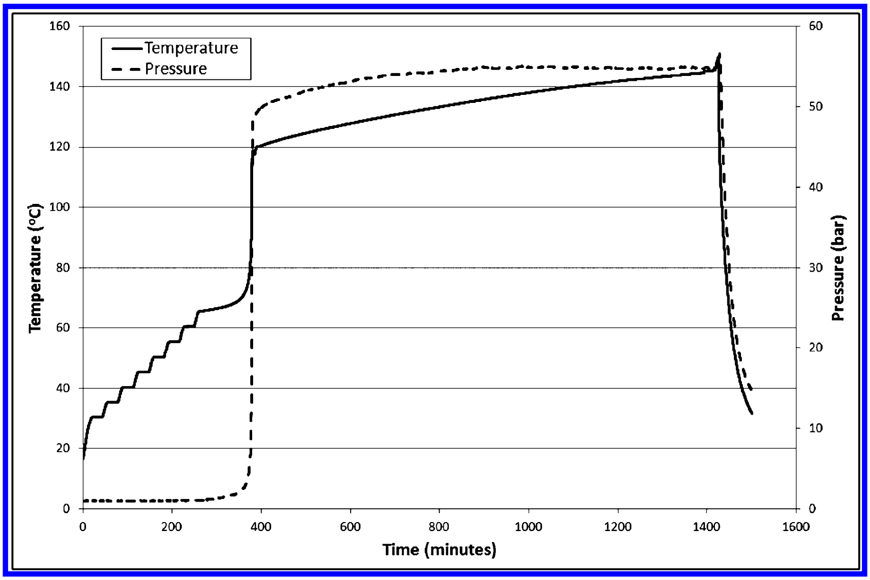


Figure 2. ARC-trace of PMB-Cl stabilized with amylene.

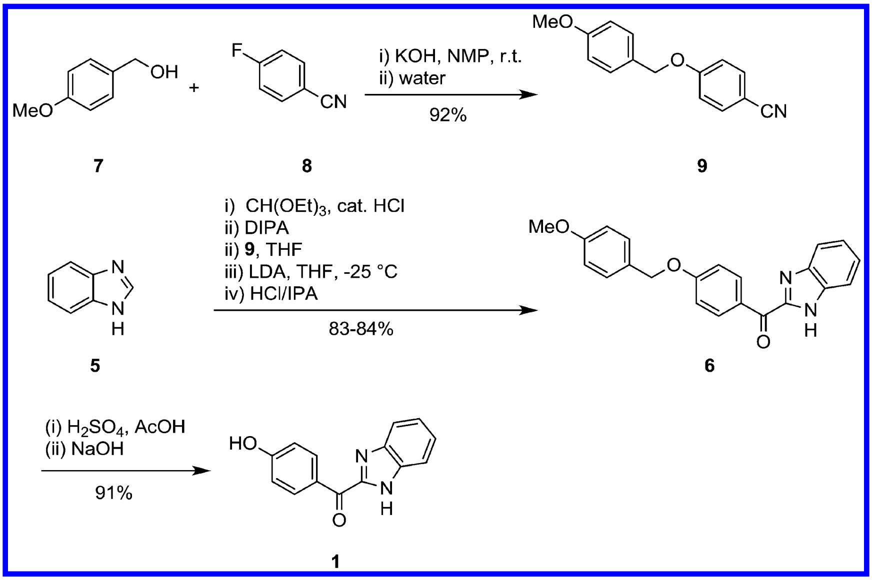
Consequently the Medicinal Chemistry route (Scheme 1) was scaled up without major issues (~ 5-10 kg batch size for the synthesis of intermediate **4**). The yield for the protection step was within the previous range (96%), while slightly diminished yields (56-58%), were obtained for the nucleophilic addition step forming ethyl ester **4**. The conditions for the deprotection were modified compared to the Medicinal Chemistry approach, in order to avoid use of the less environmentally benign solvent (dichloromethane) and acid (trifluoroacetic acid) (*vide infra*).

Second Generation Route and Process Safety Assessment

Since our route scouting towards a completely alternative bond disconnection strategy was not successful, an improved version of the original route was sought. Due to the established usefulness of intermediate **6**, it was retained as an intermediate in the synthesis towards the key building block **1**. Emphasis in a second generation route focused on the following priorities:

- replacement of PMB-Cl as a reagent
- increasing the robustness of the nucleophilic addition step
- improving conditions for the deprotection of the PMB-group

Toward these goals a three step synthesis (four isolations) of **1** was developed (Scheme 2).



Scheme 2. Second generation synthesis of ***1***

Replacement of PMBCl with PMB Alcohol

It was proposed that the use of PMB-Cl could be avoided by reversing the functionalities of the starting materials. Mechanistically the safety hazards associated with PMB-Cl are due its properties as highly reactive electrophile. Therefore it was preferred leveraging a reaction that would install the PMB-group as a nucleophile. Towards this end 4-methoxybenzyl alcohol (**7**) could be coupled in a simple nucleophilic aromatic substitution reaction with 4-fluorobenzonitrile (**8**) (Scheme 2).

The nitrile group was chosen over the ester as a carbonyl synthon because its electronic induction effect was expected to facilitate the nucleophilic aromatic substitution with PMB-OH and may allow running the ketone formation reaction at a higher temperature. Compared to esters, nitriles usually show less prevalence for formation of the overaddition products (tertiary alcohols or amines), since the intermediate metal amide formed after the first addition step is relatively stable (*9, 10*).

Process Optimization

A screen of solvents (DMF, DME, DMAc, NMP, THF) and bases (potassium phosphate, cesium carbonate, potassium carbonate, potassium hydroxide, sodium hydroxide, lithium *tert*-butoxide, sodium *tert*-butoxide, and potassium *tert*-butoxide) led to the identification of *N*-methylpyrrolidine (NMP) and solid potassium hydroxide as the ideal combination when conversion, processability and cost were considered. Potassium phosphate and potassium carbonate led to low conversions in a variety of solvents. Cesium carbonate provided acceptable results, but was deprioritized for cost and green chemistry considerations. Sodium and potassium *tert*-butoxide gave nearly complete conversions, but offered no distinct advantages over the simpler hydroxide bases. Reactions in polar aprotic solvents achieved higher conversion as compared to the reactions in the ethereal solvents, presumably due to solubility reasons. Ultimately, NMP was identified as a preferred solvent. It provided the highest solubility of the product and thereby allowed the reaction to be performed at high concentration while maintaining efficient stirring. Potassium hydroxide was preferred over sodium hydroxide based on the enhanced solubility of the byproduct fluoride salts in water. The use of aqueous hydroxide bases led to slower reactions and formation of up to 10% (HPLC area %) of the corresponding primary amide from the nitrile as a substantial byproduct.

Under the optimized conditions 4-methoxybenzyl alcohol (**7**) was added to a suspension of solid potassium hydroxide in NMP, followed by addition of 4-fluorobenzonitrile (**8**). The reaction was rapid even at room temperature (2-3 h) and the product could be isolated by crystallization by the simple addition of water, affording **9** in high yield (92%) and purity (99.7 HPLC area %, 97 wt%). The safety of this process was evaluated by performing differential scanning calorimetry (DSC) of reaction mixtures at different stages. The mixture of potassium hydroxide and **7** in NMP showed exothermic activity only between 100-107 °C, thereby assuring a large effective safety margin over the process temperature (< 30 °C).

Further evaluation of the second step allowed us to get a more detailed understanding of the intermediates and impurities formed in this reaction. The original conditions for protection employed triethylorthoformate in toluene and benzenesulfonic acid as a catalyst to afford intermediate **10** (Figure 3). The mixture's equilibrium was shifted towards product formation by azeotropic distillation with toluene. Monitoring of the reaction by HPLC was challenging due to the labile nature of the *N*-diethoxymethyl group. Monitoring by NMR showed incomplete conversion (~ 15 mol% benzimidazole) as well as formation of a byproduct: *N*-ethylated benzimidazole (**11**). This byproduct resulted in formation of impurity **12** after the subsequent addition step. It was hypothesized that this impurity results from reaction of benzimidazole with ethyl benzenesulphonate, which itself formed under the reaction conditions.

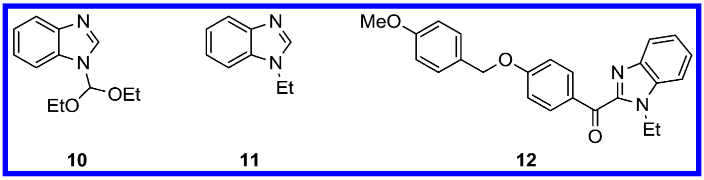
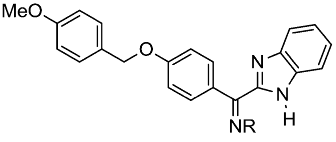


*Figure 3. Intermediate **10**, byproduct **11** and impurity **12**.*

The reaction conversion was increased to > 99 % by switching from toluene to triethylorthoformate as solvent. Formation of the alkylated impurity was suppressed by employing concentrated hydrochloric acid as the catalyst. The optimized conditions involved heating a mixture of benzimidazole (**5**) in triethylorthoformate with 2 mol % conc. HCl to 120 °C, combined with a partial solvent removal. Reactions under pure reflux resulted in higher levels of the impurity **12** (10-15 LCAP), due to formation and reaction of ethyl chloride. The acidic catalyst was quenched by diisopropylamine prior to use in the subsequent reaction step. Under these conditions conversions of > 97% were obtained without formation of alkylated impurities.

Selection of Reagent for Deprotection

A screen of bases identified lithium diisopropylamide (LDA) as a preferred base for the subsequent deprotonation of **10**. Lithium hexamethyldisilazide (LHMDS) led to incomplete conversions, while *n*-butyl lithium resulted in formation of impurities. Importantly, using the nitrile **9** as the electrophile allowed the reaction to be performed at – 25 °C, as compared to the corresponding reaction with ethyl ester **4**, which required – 78 °C for good results. The reaction was performed by in-situ deprotonation of **10**, in the presence of **9**. Reaction monitoring with React-IR demonstrated that the reaction is very fast and that complete formation of imine **13** (R = Li, Figure 4) is achieved at the end of the base addition.



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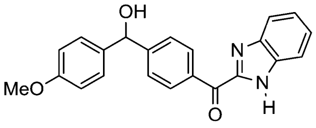


14

*Figure 4. Intermediate **13**, and impurity **14**.*

The subsequent imine hydrolysis and isolation appeared slightly more challenging. A direct quench of the reaction mixture with acetic acid resulted in a thick slurry which made efficient stirring difficult. Furthermore, the formation of a 1,2-Wittig-rearrangement product **14** was seen as an impurity under these quench conditions when an excess of LDA had been employed in the previous reaction step. The most effective quench protocol was identified as an inverse quench of the lithium imide into a mixture of aqueous 5N HCl in isopropanol, maintaining a temperature of below -5 °C. Direct crystallization of the hydrolyzed product occurred, and the material was isolated by simple filtration. Under these conditions the product was obtained in good yield (83-84%) and high purity (98.7 -99.5 HPLC area %).

Safety evaluation of this reaction sequence did not identify any signs for concern and all isolated solids were stable by DSC analysis. The benzimidazole protection step, which was conducted in a batch mode, did not display any exothermic events by ARC examination. The safety of the nucleophilic addition was ensured by the dose-controlled reaction. Under these conditions no accumulation of potentially reactive intermediates was evidenced by React-IR.

The original conditions for the deprotection of the PMB-group called for using trifluoroacetic acid in dichloromethane. We sought to replace these conditions by a more environmentally benign reagent and solvent combination. A screen of acidic media identified sulfuric acid in acetic acid as a suitable deprotection system. Alternative sulfonic acids (methane, toluene and benzene sulfonic acids) afforded similar conversions, but resulted in biphasic reaction mixtures. Use of acetonitrile, toluene, anisole or 2-MeTHF as solvents led to either decreased conversions or to less clean reaction profiles as compared to acetic acid. Anisole was introduced as PMB-scavenger to avoid formation of oligomeric and polymeric byproducts, which caused issues with product isolation.

Due to the low solubility of the target compound **1** in organic solvents, an extractive workup appeared impractical and therefore a direct isolation of the sulfate salt of **1** out of the reaction mixture was pursued. This material could be isolated directly in high yield (91-93 %) by simple filtration of the reaction mixture. The filter cake was washed with toluene in order to remove anisole and alkylated anisole derivatives. The safety of this deprotection step was evaluated via an RC-1 calorimetry study to demonstrate that anisole was effective at preventing any exothermic PMB-polymerizations (Figure 5). In this experiment sulfuric acid was added over 15 min, and the heat of reaction was measured as 85 kJ/mol, thus leading to an adiabatic temperature rise of 10 °C. The heat of reaction was deemed to be easily controllable using standard equipment, assuming an addition controlled dosing of sulfuric acid.

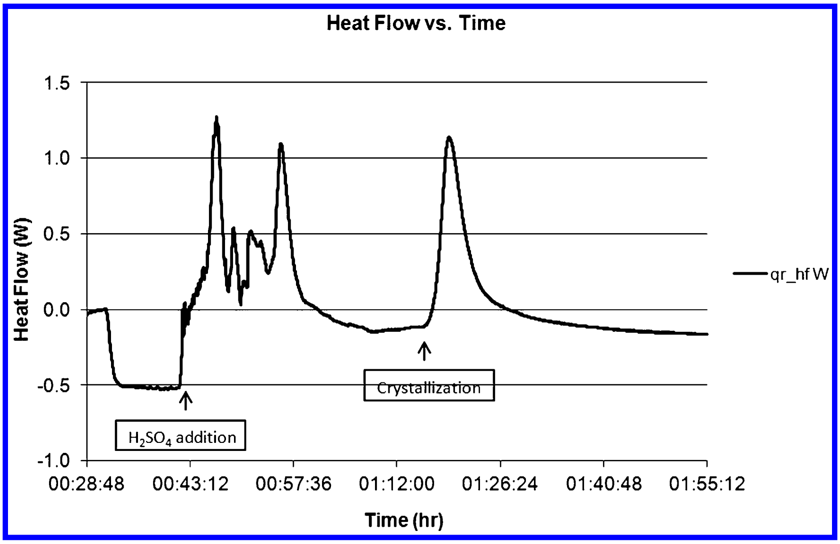
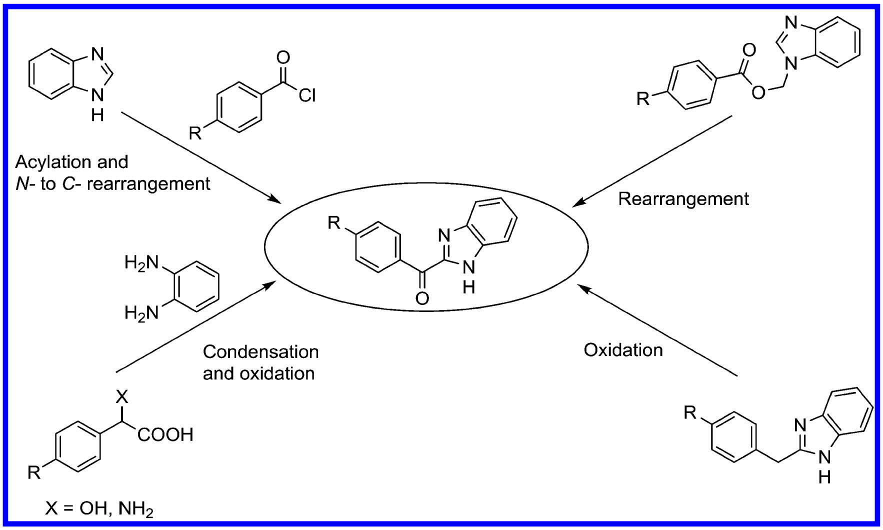


*Figure 5. RC-1 trace for deprotection reaction of **6** to form **1**.*

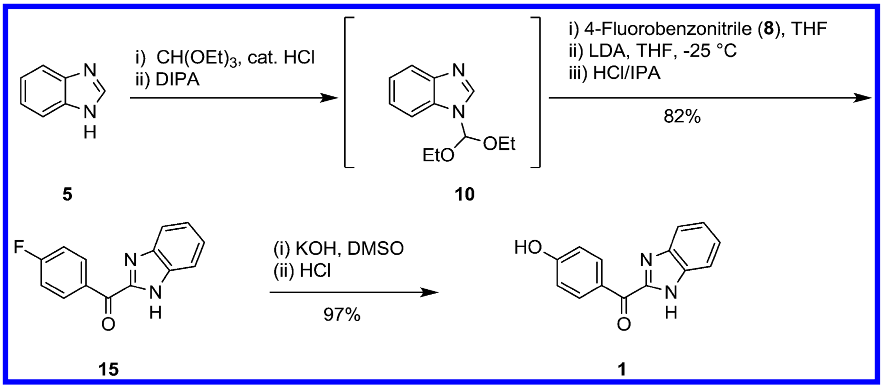
The salt break was performed by suspending the sulfate salt in water and adjusting the pH with two equivalents of sodium hydroxide. The free base formation step was a slurry to slurry transformation, but it performed robustly, and the entrainment of inorganic salts in the free base was minimal. Under these conditions free base **1** was isolated in quantitative yield and high purity (99.8 HPLC area %, 98.3 wgt %). The reaction sequence described was successfully scaled up to obtain 15 kilogram of the target compound **1**.

Final Route and Process Safety Assessment

With an enabling route to ketobenzimidazole **1** in hand to supply immediate needs, we shifted the project focus to develop a long-term route to this compound. Explorations into alternative disconnections did not reveal a superior route (Scheme 3). We therefore focused on reversing the order of reaction steps with the goal of eliminating the use of the protecting group PMB completely. This would remove the need for two steps, reduce costs of starting materials and improve the safety profile by no longer having the issue of PMB stability as a concern. Towards this end, we envisioned coupling 4-fluorobenzonitrile (**8**) directly with protected benzimidazole **10** followed by hydrolysis of the arylfluoride to afford the desired product **1** (Scheme 4). We employed the optimized conditions from the second generation synthesis for the first step to access intermediate **15**. As described earlier, a direct acidic quench of the reaction mixture again resulted in a thick slurry, which led us to use the same inverse quench protocol already in place. The procedure afforded intermediate **15** in 82% yield and 99.7–100 HPLC area %.



Scheme 3. Alternative approaches towards core structure.



*Scheme 4. Third generation synthesis of **1**.*

Evaluation of the requisite hydrolysis reaction was initiated using 4 equivalents of KOH in a 1:1 mixture of DMSO/water; however, the reaction stalled at 90% conversion even upon prolonged heating at 100 °C (Scheme 4) (*11*). Aside from the incomplete conversion, we were particularly concerned about a recent report of a highly exothermic event occurring due to the decomposition of DMSO in the presence of fluoride ion (*12*). Because of this issue a base and solvent screen in both the presence and absence of water was conducted at elevated temperatures in an effort to find safe and scalable reaction conditions.

No conversion was observed in either THF or CH_3CN. Low conversions occurred in both sulfolane and water, and use of NMP resulted in decomposition. When either DMF or DMAc was employed, 100% conversion to the undesired aminated product **16** resulted (Figure 6). We determined that it was the product of fluoride displacement by dimethyl amine, which was liberated by basic hydrolysis of those solvents. Of all solvents screened, only DMSO afforded acceptable results. Both KOH and NaOH afforded superior results to those using LiOH in various solvents. The optimal conditions were determined to be aqueous 15N KOH (essentially saturated) in DMSO at 100 °C. Under these conditions 99.7% conversion was achieved. Because we were using KOH dissolved in hot DMSO, we ran an ARC study to determine its safety profile (Figure 7).

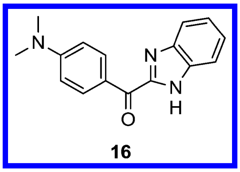


*Figure 6. Undesired dimethylamine addition side-product **16***

Our results show that at 100 °C the reaction proceeds slowly and it is not until 141 °C that an exotherm occurs. The highly exothermic decomposition of DMSO had a much higher onset temperature of 161 °C. Decomposition reactions, just like desired primary reactions, typically exhibit a rate increase with increasing temperature eventually reaching its maximum rate. The “time to maximum rate” is an important number when dealing with process safety, and is simply the time it takes the reaction mixture, from a given temperature, to reach its maximum self-heating rate. It is a temperature-dependent quantity, and can be plotted directly from the ARC data (Figure 8). The data are usually corrected for the fact that the generated heat causes a temperature rise in both the sample cell as well as the sample itself. When a log scale is used for the time to maximum rate, the result is typically a straight line which can be extrapolated to longer times if desired. The temperature at which the time to maximum rate is 24 h is defined as the T_{D24}, and this is considered a threshold temperature up to which point the thermal stability of the reaction mixture does not pose a serious problem (*13*). In this case the T_{D24} was determined to be 148 °C as shown by the extrapolation in Figure 8.

When evaluating the safety of a process, one needs to consider the adiabatic temperature rise of the desired reaction and whether a cooling failure could lead to triggering the undesired decomposition. ARC experiments showed an adiabatic temperature rise of 6 °C for the hydrolysis. A cooling failure at the desired reaction temperature of 100 °C would only give a maximum temperature of 106 °C, which is well below the measured decomposition onset of 161 °C and also well below the T_{D24} of 148 °C, offering a wide margin of safety. This placed the process in criticality class 2 in the system proposed by F. Stoessel (*11*), which rates the safety of a process on a scale of 1 to 5 based on the relative positions of the process temperature, the maximum attainable temperature of the synthesis reaction, the TD24, and the boiling point of the solvent. The lower the criticality class, the more inherently safer the process is.

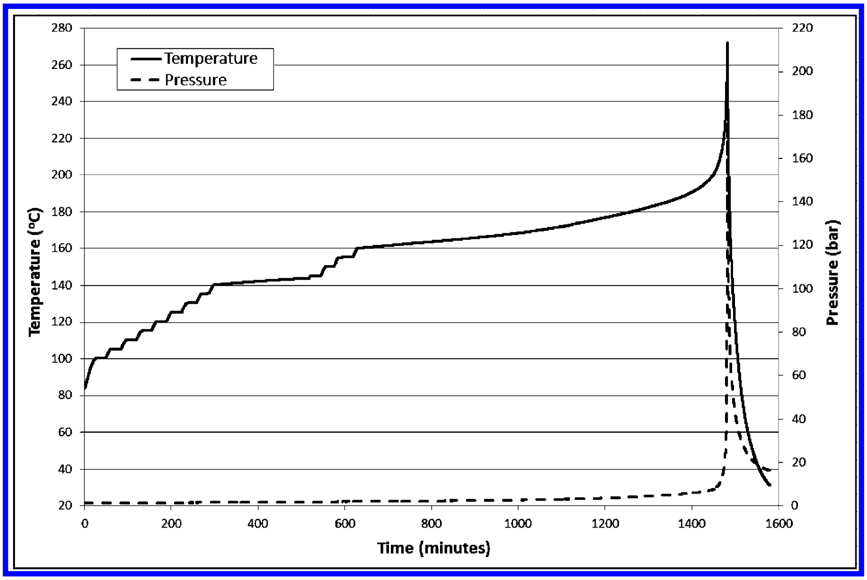


Figure 7. ARC-trace of hydrolysis reaction in DMSO.

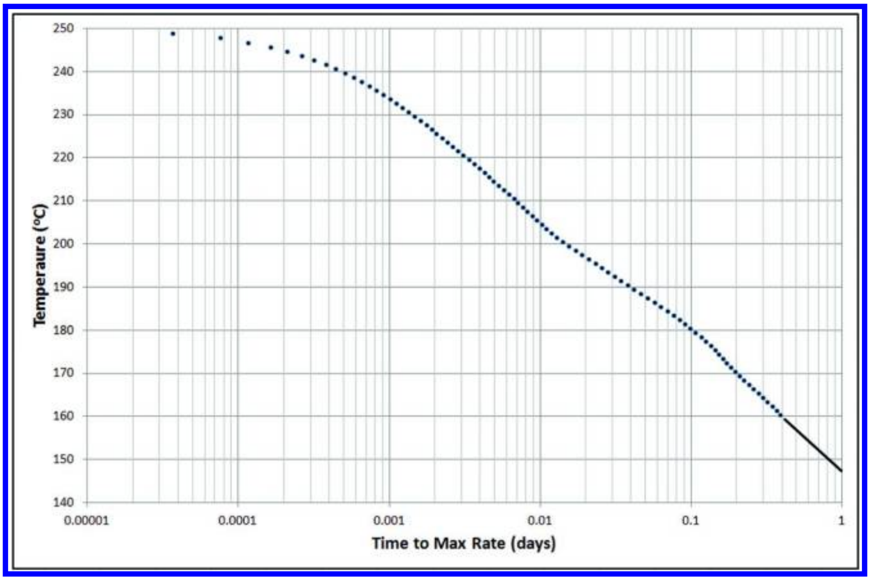


Figure 8. Plot of temperature vs. time to maximum rate and extrapolation to 24 h.

After all safety investigations and process optimization, our process was conducted as follows. The reaction was performed on 50 g scale by charging 15N KOH to a solution of ketobenzimidazole **15** in DMSO and heating the mixture to 100 °C for ca. 16 h. The mixture was cooled to 75 °C and polish filtered to remove any suspended KF. The mixture was then diluted with water and the pH was adjusted to 4 at 50 °C using 5N HCl. Additional water was added and the product was isolated by filtration after cooling to ambient temperature. Using these conditions the product was obtained (48 g) in excellent yield (97%) and adequate purity (96.8 HPLC area %).

Conclusions

Route selection and development efforts towards a key intermediate were driven by thorough safety evaluations and considerations of how to craft a safe process. In early aspects of the project, safety testing was leveraged to demonstrate absence of significant safety hazards in a fit-for-purpose delivery. Intermediate route improvements were supported by safety evaluations prior to execution of kilogram scale. Later route selection led to the discovery of a very short and efficient route (2 vs. 3 steps), which showed an acceptable safety profile (Scheme 4) (*14*).

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6. The sample of PMB-Cl was obtained from a vendor. The liquid supernatant was sampled and the ARC-test was performed without stirring. The ARC trace was recorded using the following conditions: heat-wait-seek from 30-150 °C using 5 °C steps, wait time of 15 min, and exotherm threshold of 0.02 °C/min. Samples of PMB-Cl stabilized with potassium carbonate from a different vendor was also sampled and tested. The temperature onsets were found as low as 66 °C.
7. ARC conditions: heat-wait-seek from 30-150 °C using 5 °C steps, wait time of 15 min, and exotherm threshold of 0.02 °C/min. Heterogeneous samples were stirred at 240 rpm. The pressure reading for the different samples was recorded, but cannot be used reliably since the formation of a polymeric foam led to partial blocking of the pressure sensor in some experiments.
8. The sample of PMB-Cl stabilized with amylene was obtained from a vendor. The ARC-test was performed without stirring. The ARC trace was recorded using the following conditions: heat-wait-seek from 30-150 °C using 5 °C steps, wait time of 15 min, and exotherm threshold of 0.02 °C/min.
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14. The final route was not performed beyond 50 g scale and an even more thorough safety analysis (RC-1) would have to be performed prior to scale-up to kilogram scale.

Chapter 12

Managing Hazardous Reactions and Compounds in Process Chemistry

David J. Ager[*]

PMB 150, 9650 Strickland Road, Suite 103, Raliegh, North Carolina 27615
[*]E-mail: david.ager@dsm.com

Flow or continuous processes are becoming more common to overcome process hazards, especially those associated with the use of a hazardous reagent or intermediate. This chapter discusses a wide variety of reagents that lend themselves to flow, many being generated as they are needed for the desired reaction. This also applies to hazardous intermediates. Inventories are kept as low as possible. The use of hazardous chemicals can also allow steps to be cut out of a synthesis.

Introduction

In the fine chemical and pharmaceutical industries, green and sustainable chemistry is becoming more important and flow chemistry is playing a significant role toward achieving this goal (*1*). One of the approaches available to achieve greenness is by the use of flow methods to shorten the synthetic sequence through the use of hazardous or highly reactive intermediates bit accessible in a batch process (*2*). Low temperature reactions, for example, can be performed in small reactors where the majority of the cooling is used to counteract the reaction exotherm; a large batch reactor does not have to be cooled. However, these approaches can involve the use of a hazardous reagent or intermediate. Batch methods can suffer from, as examples, low heat transfers, extended reaction times, and inadequate mixing. These limitations can be very important when using a hazardous material.

Flow chemistry has been in use for decades, especially in the arenas of petrochemicals and large-scale commodity chemicals. It is not a new concept for smaller scale reactions (*3*). Scaling down the equipment and processes for organic

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chemistry has been a challenge, but these are now being overcome (*4*, *5*). The range of reactions becoming available is increasing. For example, a flow system allows the use of high temperature reactions without significant degradation (*6*). Flow is becoming more popular in medicinal chemistry where different molecules can be made each separated by a blank slug of solvent (*7*). The use of a flow system can also be used to extract kinetic data (*8*).

Perhaps the ultimate flow system for the pharmaceutical industry is to have a set up where the starting material chemicals are added at one end and the final form of the active drug emerged from the other end (*9*).

There are a number of companies that supply laboratory, pilot scale and manufacturing (usually up to a few tons) equipment. They cover reactors, mixers, separators and handling of two- or three-phase systems. The reader is directed to comprehensive reviews for background material on microfluidics and flow reactions as well as equipment design which has not been included in this chapter (*10*, *11*).

While equipment that can be used to monitor flow reactions is not covered, references will be made to novel or specific uses. Similarly, references will be made to critical analytical methods that are required to optimize yields through, for example, injection of a reagent at the appropriate time or to ensure complete reaction of a hazardous component in the reaction mixture.

This chapter will concentrate on the uses of hazardous reagents, including their preparation "on demand" and hazardous reactions. If the product of the reaction is unstable, such as an explosive of which nitrate esters and tetrazoles are examples (*vide infra*), it will only be included if there is a life science application for it. Although many schemes follow "traditional" representations, all examples in this chapter are conducted in flow, unless otherwise noted.

The collaboration of engineers is often important, as they are more familiar with process safety controls. A good example is handling of gas evolution. An uncontrolled decomposition of a mole of diazomethane will produce a mole of nitrogen and a concurrent rise in pressure, which may be very dangerous. This must be contained within the apparatus or be safely vented. Chemical engineers are also more familiar with the bulk properties of liquids and parameters, such as Reynolds numbers, to determine what type of flow will be observed in the apparatus. For most of the examples in this chapter, turbulent flow is desired (high Reynolds numbers) (*11*, *12*).

Flow or continuous chemistry at the scale used for pharmaceutical applications is a rapidly growing area with some reactions beginning to achieve maturity. Most topics will include speculation on the future of flow, areas for improvement and specific challenges for this specific area of chemistry.

Unsaturated Nitrogen Compounds

The largest class of compounds that have been employed in flow reactions involve unsaturated nitrogen compounds, such as azides and nitro-containing compounds. Due to their reactivity, this class of compounds provides a plethora of useful synthetic methods. Unfortunately, many these compounds are unstable and some are explosive. Flow chemistry minimizes such dangers by enabling the production of only small quantities of reactive intermediates.

Diazo Compounds

Diazomethane

Diazomethane has well known safety problems including toxicity and stability issues, which can lead to an explosion. A number of precursors can be used to generate diazomethane (*13–15*), most of which are *N*-nitroso amines. These precursors have their own safety issues, as they can be potent carcinogens as well. The procedure for the nitrosation can be performed in a flow system to reduce safety issues (*16*); thus, two reactions can be coupled together.

Flow systems have been devised to allow the production and subsequent reaction of diazomethane, thus keeping the reactor inventory low and avoiding workup or isolation of the diazomethane. This led to the move to flow reactions rather than making a batch process safer (*17*, *18*).

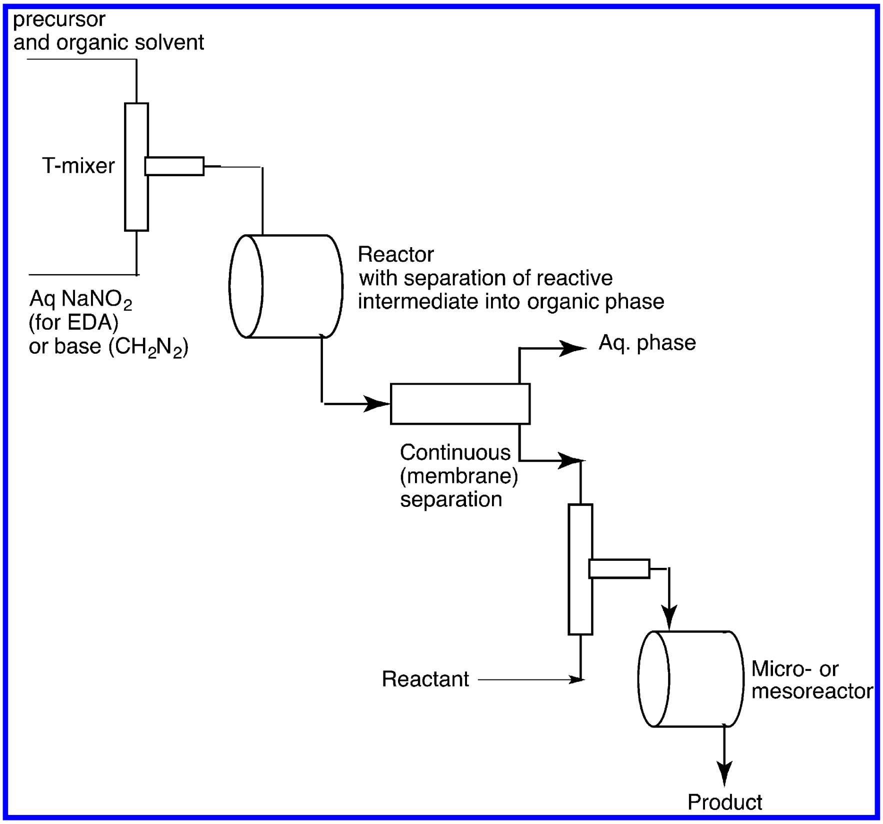
Diazomethane and the closely related diazo esters (see Section on Diazo Esters) can be prepared in flow with a membrane separator to produce the diazo compound in an organic solvent (Scheme 1) ready for further reaction (*19–21*). The membrane separator facilitates the phase separation, allowing this to be part of the flow sequence.

One of the best-known applications for diazomethane is the preparation of cyclopropanes. An example is given in the following section, as the use of diazo esters for preparing substituted cyclopropanes is much more popular than the parent system.

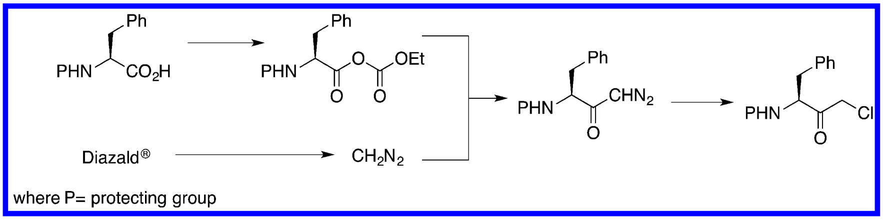
Diazomethane can be used for the homologation of acids to α-substituted ketones. This reaction has been performed at scale in flow for the preparation of chloroketones intermediates used in the synthesis of HIV protease inhibitors (Scheme 2) (*13*).

The reaction of aryl diazo compounds with ethyl vinyl ether provides monoarylated acetaldehydes (*22*). The use of chlorosulfonate provides arylsulfonyl chlorides (*23*). Phenols, aryl chlorides, bisaryl and unsymmetrical aryl diazo compounds can also be prepared (compare with Scheme 20 in Azide Section) (*24*). A Diels-Alder reaction between benzyne, prepared from anthranilic acid using *tert*-butyl nitrite and furan; the reaction was monitored by mass spectrometry (*25*).

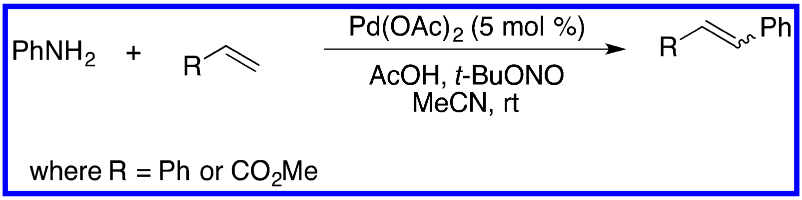
A Heck coupling has been achieved with aryl bromides, iodides or diazonium salts of an aniline (*26*). The use of segmented (plug) flow in a microreactor can increase the reaction rate. This is illustrated by a Heck reaction with a diazonium salt as the precursor (Scheme 3) (*27*).



Scheme 1. Schematic generation of diazomethane or ethyl diazoacetate in flow.



Scheme 2. Preparation of an α-halo ketone used as an HIV protease inhibitor intermediate.

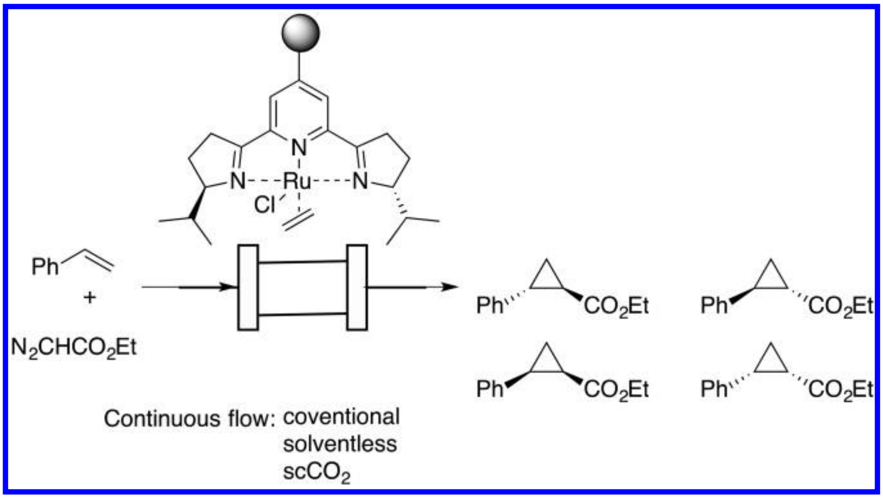


Scheme 3. Heck reactions using homogeneous segmented flow conditions.

The versatility and reactivity of diazomethane and higher analogous make these compounds very useful in synthetic sequences. Their use often allows shorter reaction sequences to be employed, in keeping with green and sustainable chemistry. Care has to be exercised when choosing a precursor as some of these have human health issues, such as *N*-nitroso compounds. However, performing the reactions in flow removes most of these issues. The methodology to prepare diazo compounds is maturing and will continue to grow with optimization of membranes for better separations of phases.

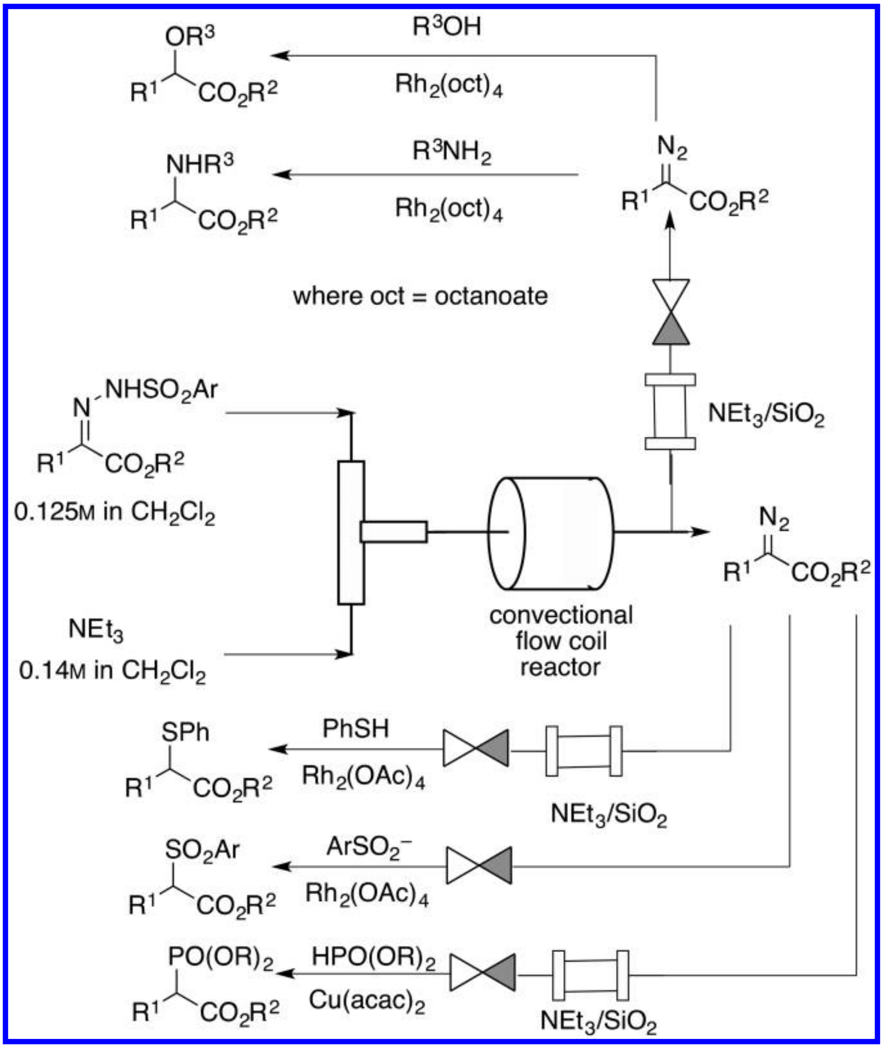
Diazo Esters

As mentioned above, perhaps the best-known use of diazo compounds is to prepare cyclopropanes. The diazo compound is typically converted to a carbene, which subsequently adds to alkenes to form the corresponding cyclopropanes. There are many ways to achieve this but the use of ruthenium catalysts has become a standard method. The carbene intermediate readily undergoes dimerization and hence a large excess of alkene is often used to minimize this side reaction. The use of flow can help with the recycle of excess alkene. The use of supercritical CO_2 has also been to shown to have some advantages, such as being a green solvent that is simple to remove (Scheme 4) (*28*).



Scheme 4. Cyclopropane formation.

Although EDA decomposes rapidly in the presence of a catalyst such as Rh or Ru, it does not require immediate reaction when in solution and can be used at scale (see Simpson Chapter). The versatility of diazo esters is also not limited to the preparation of cyclopropanes, they are also used to access a variety of α-hetero substituted esters as illustrated in Scheme 5 (*29*, *30*).



Scheme 5. Formation and reactions of diazo esters.

Ethyl diazoacetate with an aldehyde in the presence of $BF_3 \cdot OEt_2$ gave β-keto esters, which were then converted to 2,6-disubstituted pyrimidin-4-ols by reaction with amidines (*31*).

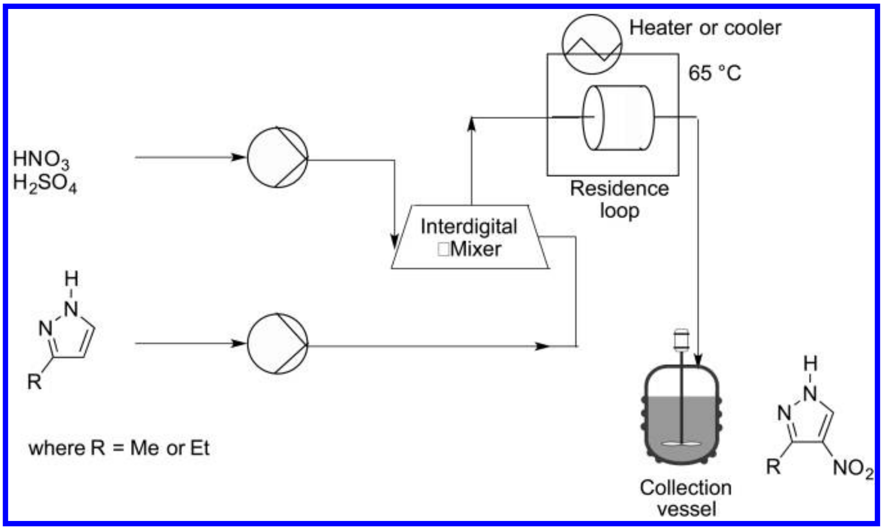
Similar to the parent diazoalkanes, diazo esters are also versatile and very useful intermediates in organic synthesis. The methodologies compounds are becoming more established and mature. Their use in flow continues to grow because of the ability to use cascade of reactions, to avoid their isolations as well as the optimization of membranes for separation of phases.

Nitrations

Nitration has long been a standard method for the introduction of a nitro group into an aromatic compound. Anions derived from nitro alkanes have found use as nucleophiles for aldol-type and Michael addition reactions. The nitro group can be converted to a carbonyl functionality by a Henry reaction or reduced to provide an amine. The aromatic reactions can become runaways due to autocatalysis and over-nitration leading to potential explosions (*32*). The problem is exacerbated if multiple nitrations are required, as in picric acid or trinitrotoluene.

The use of flow has been used to reduce the safety hazards associated with nitration reactions. However, it will not remove the inherent instability of a product. Flow allows the use of fuming nitric acid (*33–35*) even with acetic acid, which causes an explosion hazard. The most common acid catalyst for nitrations is sulfuric acid. Conditions can be varied so that a mononitro aromatic derivative is almost the sole product (*36*, *37*). An example is the nitration of benzaldehyde using nitric acid and a catalytic amount of sulfur acid in which efficient mixing was an important factor (*38*). Pyridine has been nitrated on large scale using this approach (*39*). Acetic acid was used as the acid catalyst in the nitration of salicylic acid (*40*).

As with other examples, electron rich aromatic compounds can be nitrated with nitric acid in the presence of sulfuric acid. The simple system is shown in Scheme 6 (*41*).



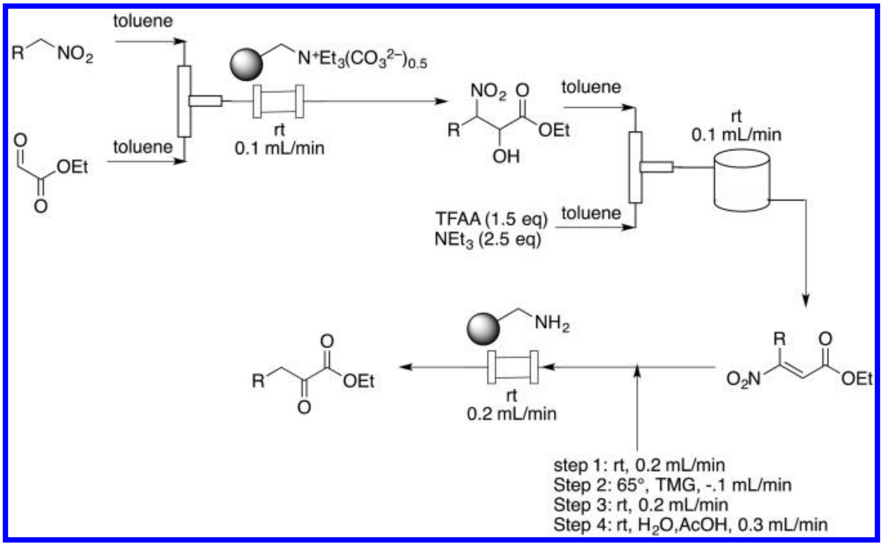
Scheme 6. Representation of a flow nitration apparatus.

In a synthesis of an agrochemical intermediate a dinitration was performed with various ratios of aniline to nitric acid. The highest yields were observed with a 3:1 nitric acid:aniline ratio, a lower temperature (60°C) and a short residence time. The aniline, 3,4-dimethyl-*N*-(pentan-3-yl)aniline was mixed with nitric acid in mixing micropores, which were directed connected to residence microchannels to give 3,4-dimethyl-2,6-dinitro-*N*-(pentan-3-yl)aniline. The product, *N*-(3,4-dimethyl-2,6-dinitrophenyl)-*N*-(pentan-3-yl)nitrous amide, from trinitration was also formed, but at a lower level than for other reaction parameters monitored (*42*).

Nitro compounds are useful intermediates as they can be used in a wide variety of reactions. The ones discussed below have all been adapted to be used in flow giving the potential for sequential transformations.

Nitro compounds can be reduced to the corresponding amines in flow using catalytic hydrogenation (See also Hydrogenation Section) (*43–48*). In addition to hydrogen, formic acid can be used as the reductant. This approach was used for the reduction of *p*-nitrophenol with the catalyst plated on the reactor wall (*49*).

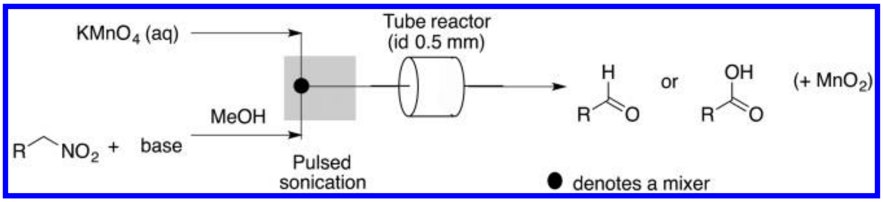
Unsaturated nitro compounds are good Michael acceptors and this reaction has been adapted for use in flow processes (*50–52*). The process can be asymmetric (*53*). Rather than using a 1,4 conjugate addition, direct 1,2-addition to a carbonyl group can also be achieved. This is illustrated by a procedure to α-ketoesters that can be prepared from nitroalkanes by reaction with ethyl glyoxalate (Scheme 7) (*54*). The unsaturated nitro moiety is then converted to a carbonyl group.



Scheme 7. Preparation and use of a nitroalkene.

As stated above, nitro compounds can be used in nitroaldol and conjugate additions. However, very little has been published on the use of these reactions in flow to date.

Oxidation of a nitro compound with potassium permanganate provides the carboxylic acid or aldehyde (Scheme 8). The use of ultrasound pulses avoids blockage due to the insoluble MnO_2 particles (*55*).



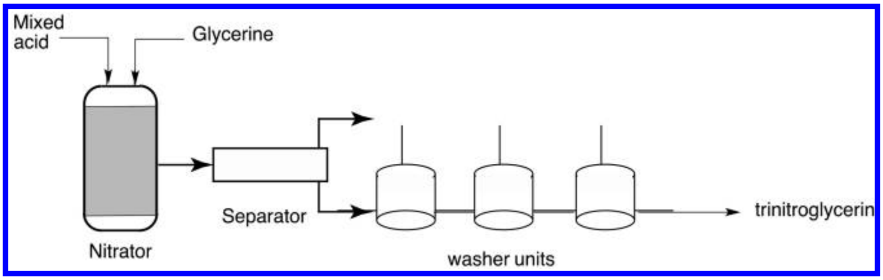
Scheme 8. Conversion of nitro compounds to carboxyl compounds.

Nitrations have been around for many years but only until recently has technology found an efficient means to ameliorate the inherent hazards of nitration. Flow methodology offers a much safer way of controlling the reaction conditions and even what might be considered simple reactions are being performed using this methodology. As the reaction mechanisms and other reaction parameters are well understood, this application should continue to grow.

Nitrate Esters

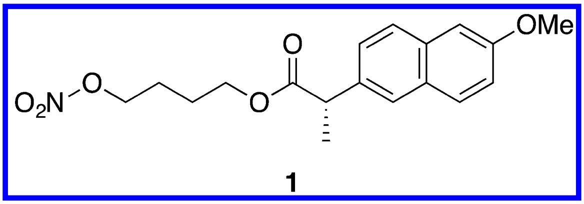
Nitrate esters have both industrial and biological applications, such as trinitroglycerin, but they can be unstable. In this case trinitroglycerin is the explosive in dynamite. This class of compounds has traditionally been called nitro compounds, although they are actually nitrate esters. The instability of the products, especially under the harsh reaction conditions used to prepare them, lends a basis to explore flow technology.

Nitric acid with sulfuric acid catalysis has been used to make the nitrate ester of *iso*-octanol (*56*). Trinitroglycerin can be prepared by a flow method as heat control is very important (Scheme 9). The instability of the product once collected at the end of the flow system is still present and must be handled with care (*57*).



Scheme 9. Apparatus for making trinitroglycerin. (Modified from Biazzi NG Plant, 1973 information)

DSM has recently successfully scaled-up in a flow micro reactor that conducts a hazardous nitrate ester synthesis to produce significant quantities of the API naproxcinod (**1**) under current good manufacturing practice (cGMP) standards. Twenty-five tonnes of material were processed in only four weeks. A Corning flow reactor was used for smaller amounts but then silicon-carbide reactors from ESK were used for the bulk manufacture (*58–60*). The key parameters for success were turbulent mixing and the solubility of the mono-ester in the organic solvent, which essentially removed it from the acidic reaction phase. The nitration is performed with highly concentrated nitric acid removing the need for sulfuric acid as a catalyst.



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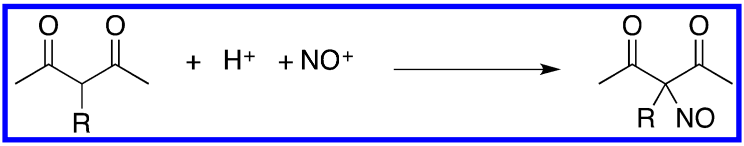
Nitrate esters are popular targets in organic synthesis because of their wide applicability. Flow offers a good method for their preparations by controlling the reaction exotherms. This area should continue to expand when one considers how useful it is to introduce nitrogen into starting materials.

Nitrosations

Nitroso compounds are useful for accessing a wide range of functionalized compounds. There are many methods to prepare these compounds (*61*). A flow method has been used to access α-nitroso-β-diketones (Scheme 10) (*62*).



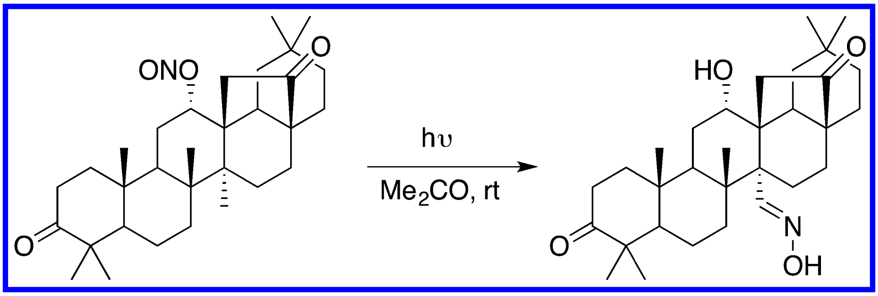
Scheme 10. Preparation of α-nitroso-β-diketones.

Nitroso compounds, including acyl nitroso compounds, can undergo Diels-Alder reactions under microflow conditions. Improved yields, compared to batch methods, result from better control of the reaction parameters (*63*).

Like nitration, nitrosation is very old chemistry. While it is not as popular as nitration, some of the more specific applications discussed below have good potential.

Nitrite Esters

Nitrite esters can be decomposed by light, for which a flow system with a narrow cross-section is advantageous (see Photochemistry section under Singlet Oxygen). An example is the Barton reaction where "remote" functionalization in a steroid can be used to efficiently convert an unreactive center into one that can be used for further reaction (Scheme 11) (*64*). One of the advantage of a flow approach is the increased efficiency of the photochemical reaction.

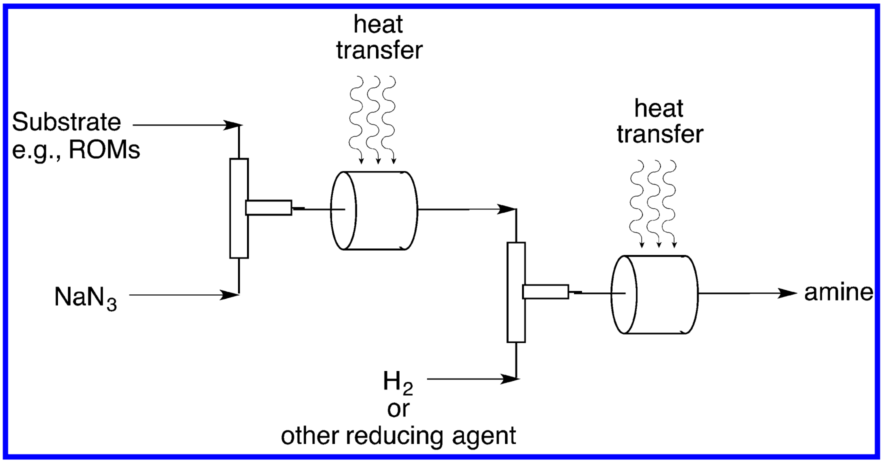


Scheme 11. Photochemical Barton reaction.

Nitrite esters have found little use to date. The reaction of Scheme 11 uses the advantages of flow for photochemical reactions rather than to mitigate safety issues. Advancement with these compounds will rely upon more applications of the nitrite esters.

Azides

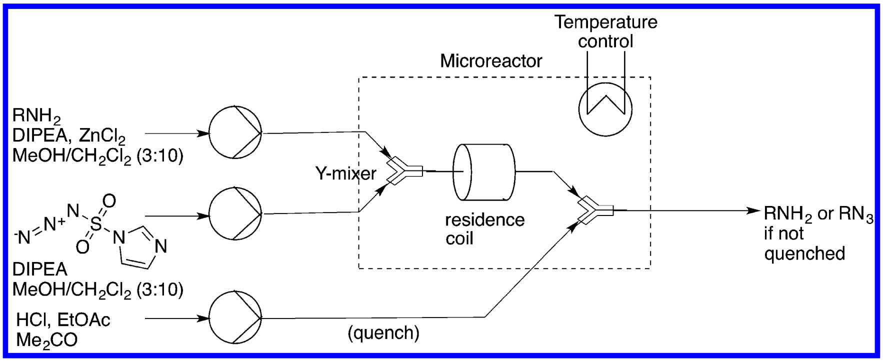
Due to their explosive nature, azides (see Archibald Chapter) have had limited application outside of laboratory settings (*65*), and in uses where their explosive properties are desired. Some drugs rely on the properties of azides, such as azidothymidine (AZT). The common method of preparation is the displacement of leaving groups derived from alcohols, such as sulfonate esters, by an inorganic azide (Scheme 12). Substitution of a halogen is also a useful route (*66*). However, their preparation can sometimes be difficult and may require high temperatures (*8*, *67*, *68*).



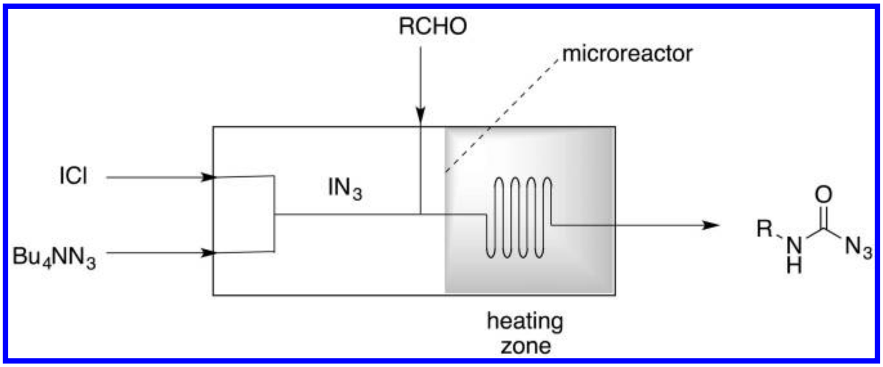
Scheme 12. Conversion of a mesylate or similar substrate to an amine.

The safety issues have led to the use of flow for reactions involving azides. The resultant organoazides from the initial substitution are useful intermediates to access amines, by cycloaddition—click chemistry (*69*) as popularized by Sharpless (*70*). In-line FT IR can be used to monitor the reactions, as the azide group has a strong IR absorption.

There are other ways of accessing azides. One such method that has been adapted to flow utilizes a diazo transfer reagent (Scheme 13) (*71*). Iodoazide can be used to prepare acyl azides, which are intermediates in Curtius rearrangement (*vide infra*) (Scheme 14) (*72*). The products can then be taken on for further reaction. The use of flow keeps inventories of the unstable compounds to a minimum, allowing efficient control of the usually exothermic reactions and reduces hazards.



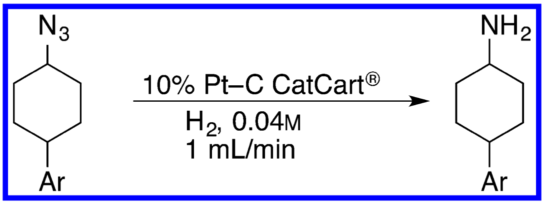
Scheme 13. A schematic view of the microreactor setup



Scheme 14. Preparation of an acyl azide.

Amine formation

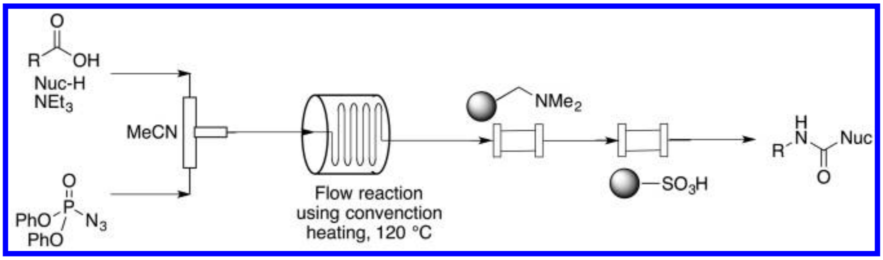
An azide can be reduced to a primary amine by catalytic hydrogenation (see also Hydrogen Section). For smaller scale work, an H-Cube can be used. This procedure was used to make a library of compounds (Scheme 15) (*73*).



Scheme 15. Preparation of amines from azides.

Circumventing the amine, an azide can be coupled with a thioacid to form an amide. The use of flow keeps the concentration of azide to a minimum (*74*).

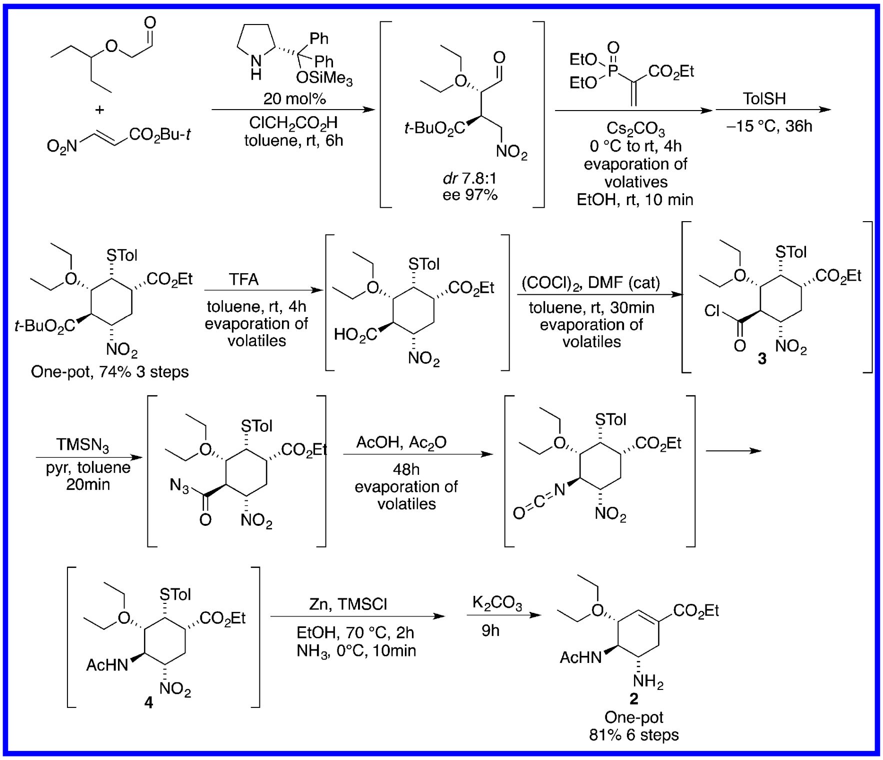
In a Curtius rearrangement where a carboxylic acid is converted to an amine, the risks of handling azides can be reduced by putting the azide on a monolith column (*75*). Diphenyphosphoryl azide is a common reagent to perform a Curtius rearrangement with carboxylic acid substrates. The intermediate isocyanate can be trapped with a variety of nucleophiles (Scheme 16) (*76*). In the process an acyl azide is formed.



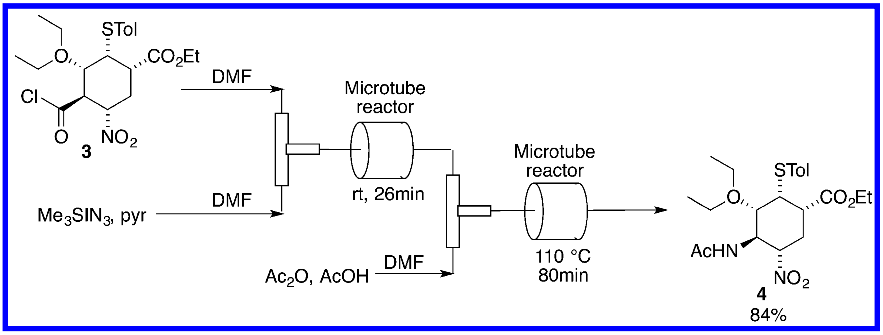
Scheme 16. General scheme for the Curtius rearrangement of carboxylic acids under continuous flow conditions.

A Curtius rearrangement still has many safety issues. The use of flow can mitigate many of these (*77*), and including a FT IR module placed in-line, can be used to monitor the reaction (*78*). The approach has been used to prepare (–)-oseltamivir **2** (Scheme 17). The approach to **2** also uses a nitro group as an amine precursor, but flow methodology is not employed for that step. The procedure has been modified to use a flow reaction for the Curtius rearrangement starting from the acid chloride intermediate **3** (Scheme 18) (*79*).

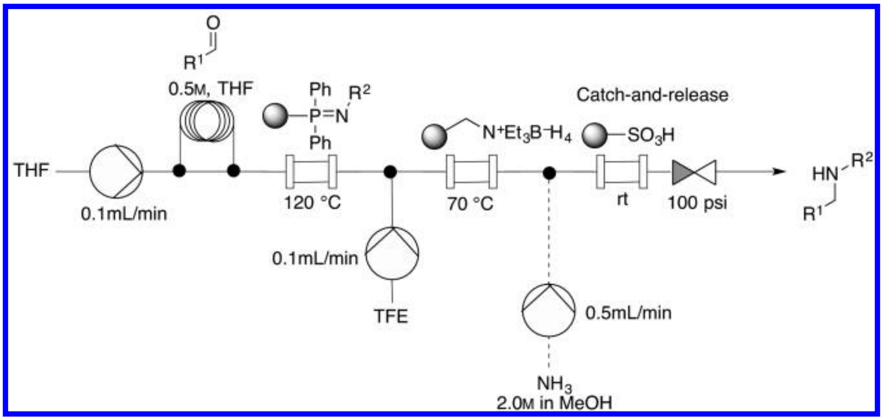
An aza-Wittig reaction has been used to prepare amines with a catch-and-release method allowing purification of the product (Scheme 19) (*80*). The aldehyde is introduced through a sample loop and then pumped through an iminophosphorane monolith that has been preloaded in a separate step. A monolithic column has porous channels rather then beads allowing it to be used under pressure, The resultant imine is then reduced by a borohydride monolith (see Metal Hydrides under Reductions). The product amines were purified by being trapped on a sulfonic acid monolith, allowing the impurities to be washed out, and then released by aqueous ammonia in methanol.



*Scheme 17. Sequence of two one-pot batch reactions for the preparation of (–)-Oseltamivir (**2**).*

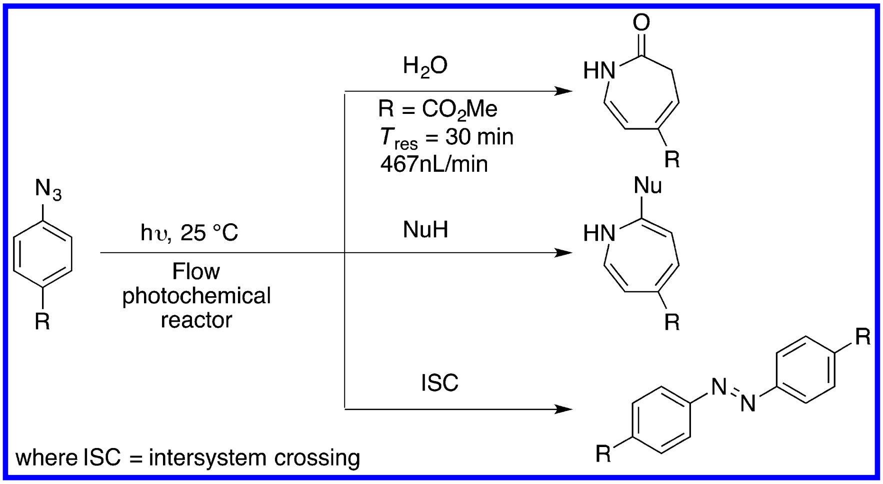


*Scheme 18. Synthesis of intermediate **4** from **3** by use of a flow system.*



Scheme 19. Automated flow process for aza-Wittig reaction, imine reduction and purification.

A flow photochemical reaction can be used to prepare cyclic amides or lactams from aryl azides. The use of flow minimizes side reactions such as the formation of diazo compounds (Scheme 20) (*81*). This technique is a general method for lactam formation, however, some modification of reaction conditions will be needed.

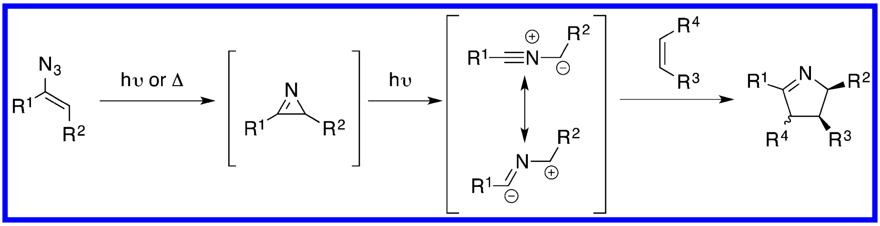


Scheme 20. Photolysis of aryl azides.

With their inherent instability but their synthetic usefulness, azide formation and reaction has been a major area of work as flow has been adapted into a mainstream technique. The methods for use of flow are now in place, and the ability to couple azide formation with downstream chemistry covers a wide range of reactions. This means that the use in flow for this class of compounds is becoming mature. The number of applications and reactions should continue to grow steadily.

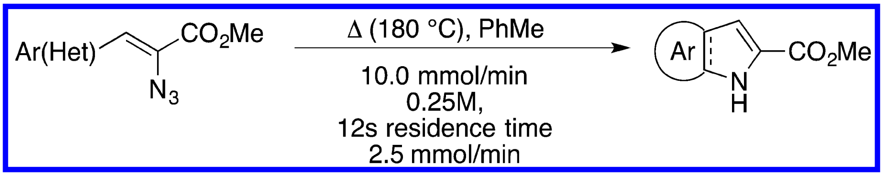
Heterocycle Formation

The photochemical degradation of vinyl azides has been used to prepare 1,2-dehydropyrroles by a cycloaddition with an alkene (Scheme 21). The approach can be modified to prepare triazoles and tetrazoles. The intermediate azirine can also be isolated (*82*).



Scheme 21. Formation of azirines from vinyl azides and 1,3-dipolar cycloaddition to a pentacyclic N-heterocycle.

Pyrroles and indoles are available by pyrolysis of a carboxy vinyl azide. The methodology is illustrated by the synthesis of a pharmaceutical intermediate to a DAAQ inhibitor, where Het is furfuryl (Scheme 22) (*83*).



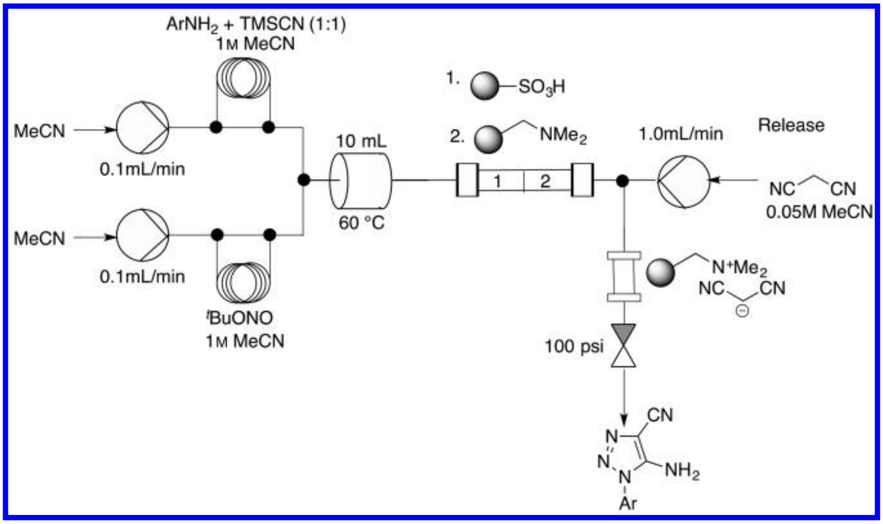
Scheme 22. Continuous flow synthesis of bicycles.

In addition to the pyrrolidines illustrated in this section, these comments also relate to triazoles and tetrazoles. The latter classes have more safety issues due to the high nitrogen content. The approaches to *N*-heterocycles from azides employ established chemistry. The application in flow mitigates many of the safety issues. It would seem, therefore, that the number of applications and reactions will continue to grow as the enhanced safety factor reinvigorates an existing reaction.

Triazoles

The ability to control the regioselectivity of the cycloaddition by the choice of an appropriate metal catalyst can increase the use of azides as intermediates.

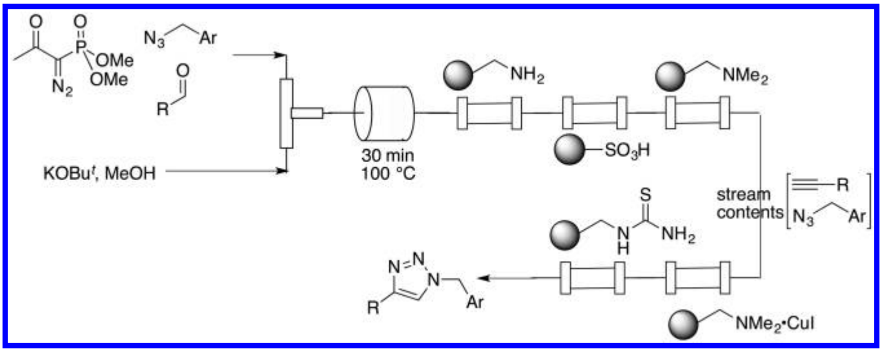
ReactIR has been used to monitor the presence of azide to optimize reaction conditions as well as improve safety (*78*). This approach was used in a synthesis of 5-amino-4-cyano-1,2,3-triazoles (Scheme 23) (*80*, *84*).



Scheme 23. Flow synthesis of 5-amino-4-cyano-1,2,3-triazoles.

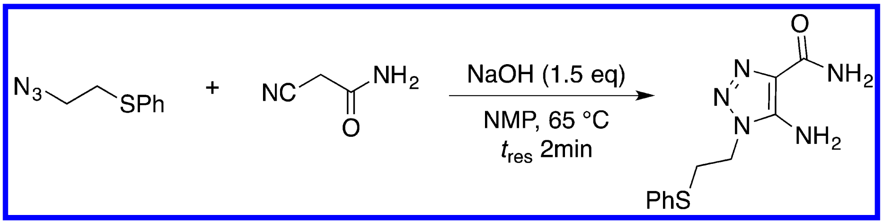
There are a number of examples of the cycloaddition of an azide to an alkyne. Most of the examples discussed use a copper catalyst in the formation of triazoles (*85–92*). The copper can be part of the reactor (*85*) or an additional reagent (*93–96*).

Triazoles are available from aldehydes in two-steps and alcohols in 3 (Scheme 24) (*97*). These methods include flow reaction methods for azide formation. The alcohol scheme has an extra step as a TEMPO oxidation is performed with an additional cartridge. The order of the other cartridges is slightly changed.



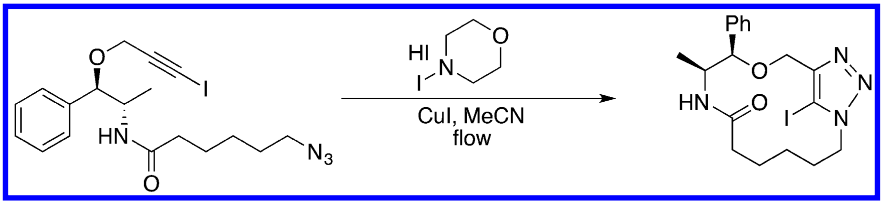
Scheme 24. Preparation of triazoles from aldehydes.

Ethyl azide is a hazardous material to handle. The use of flow and the inclusion of a phenylthio group allow its safe use in a cycloaddition approach to triazoles (Scheme 25). The thio group can be removed later by a Raney nickel reduction (*98*).



Scheme 25. Preparation of triazoles from an ethyl azide equivalent.

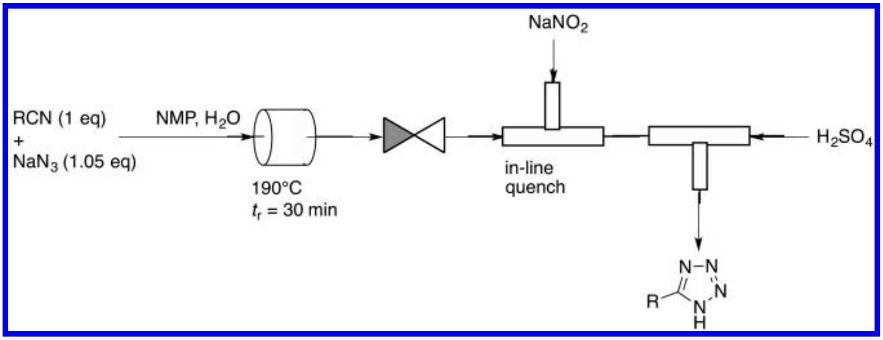
The use of azides can be adapted to make macrocycles by a ring closing cycloaddition (Scheme 26) (*99*, *100*). The reaction is intramolecular rather the bimolecular reactions described above.



Scheme 26. Synthesis of a macrocycle by an azide cycloaddition.

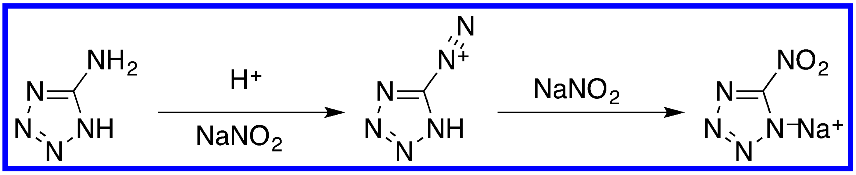
Tetrazoles

Tetrazoles can be unstable, especially when nitrogens make up most of the weight in the product. The cycloaddition of an azide to a nitrile provides a useful entry to tetrazoles (Scheme 27) when performed in flow (*101*, *102*). The reaction can be performed at high temperatures in the flow system in a much safer manner than in batch-mode (*103*).



Scheme 27. General method for the preparation of a tetrazole.

A two-step Sandmeyer-type reaction has been used to prepare nitrotetrazole (Scheme 28), a compound with a high nitrogen content that would otherwise be hazardous to consider making in batch mode. Mixing is laminar in a flow system (*104*).



Scheme 28. Preparation of sodium 5-nitrotetrazole.

Vilsmeier Reagents

Although useful as synthetic intermediates, safety issues have limited their usage in batch. Flow, therefore, should increase their usage and flexibility. A traditional Vilsmeier-Haack reaction is the substitution of an activated position on an aromatic compound with a formyl group to afford the corresponding aldehyde. The reaction can be performed in flow to minimize the inventory of the unstable reagent (*105*).

One application of these reagents is the transformation of carboxylic acids to the corresponding acid chlorides with the Vilsmeier reagent being formed under flow conditions from a formamide and phosgene (*106*).

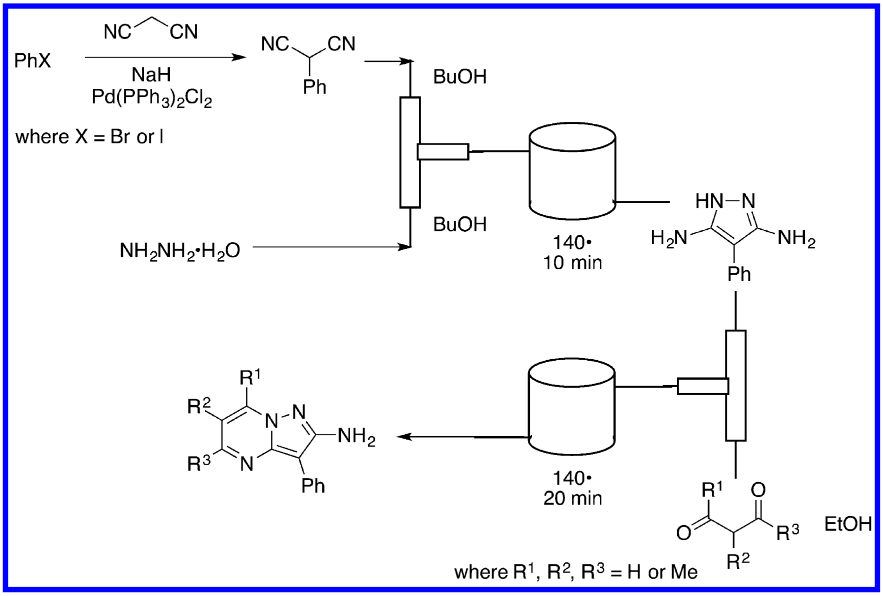
As there are alternatives to these reagents, with many of these being applicable to flow chemistry, this class of compounds will likely only see growth for specialized applications or will be made and used immediately.

Hydrazine

Although hydrazides do not contain unsaturation, they form derivatives such as diimides that do. Hydrazine is an explosive compound especially when not in solution (see Chapter on Hydrazine).

In addition, hydrazine is a reductant and a source of N-N moiety in the synthesis of heterocyclic compounds. The use of flow can alleviate some of the safety concerns.

The reaction of hydrazine with malononitriles and 1,3-dicarbonyl compounds was used to prepare pyrazolo[1,5-*a*]pyrimidines. The dicyanide moiety (2-phenylmalononitrile) was introduced first followed by the addition of hydrazine (Scheme 29). The initial product, 4-phenyl-1*H*-pyrazole-3,5-diamine, is then reacted with either malonaldehyde or pentane-2,4-dione to form 3-phenylpyrazolo[1,5-*a*]pyrimidin-2-amine or 5,7-dimethyl-3-phenylpyrazolo[1,5-*a*]pyrimidin-2-amine respectively. This reaction sequence was performed in flow (*107*).



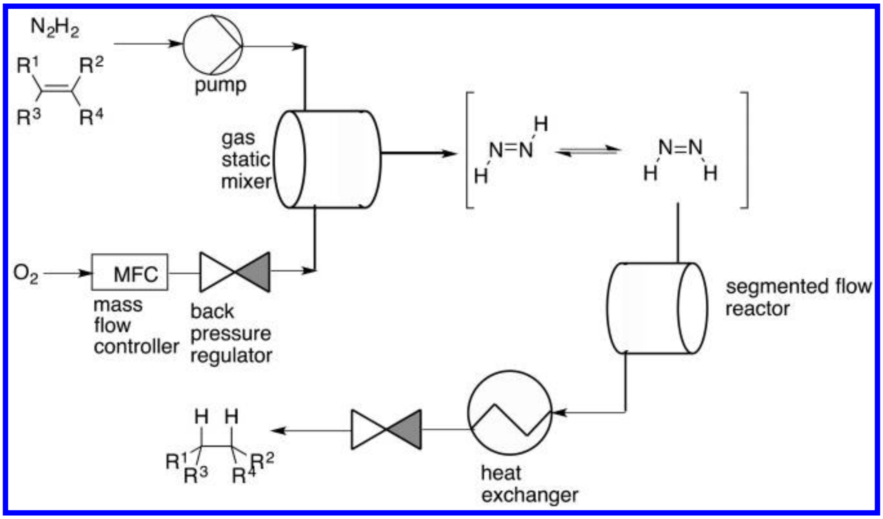
Scheme 29. Flow synthesis of 5,7-dimethyl-3-phenylpyrrazolo[1,5-a]pyrimidin-2-amine

Other heterocycles such as *N*-aryl pyrazoles (*108*), 1,2-azoles (*4*, *109*) and substituted indazoles (*110*). were also prepared by flow reactions.

The reduction of diazonium salts results in the formation of *N*-arylhydrazine, which can be used to prepare heterocycles. These transformations can be performed in flow (*111*).

Hydrazine is a precursor to diimide by an oxygen oxidation. The diimide is a reductant for alkenes (Scheme 30) (*112*). The main reactor has segmented flow. Thus, diimide can be used to reduce alkenes in the absence of hydrogen.

The diimide can also prepared by a coupling reaction from hydroxylamine and *N,O*-bistrifluoroacetylhydroxylamine (*113*).



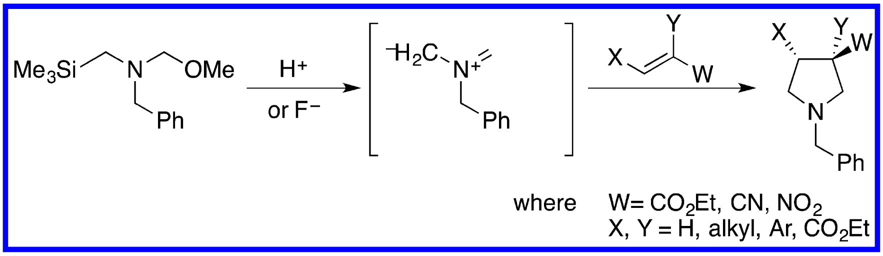
Scheme 30. Reductions with diimide.

Hydrazine is becoming a useful reductant that may be used as a hydrogen alternative. Because of the low cost and ready availability of hydrogen gas, hydrazine will, no doubt, remain the second choice outside of specialized applications. However, that should not detract from its usefulness, especially since flow can minimize safety issues.

Azomethines

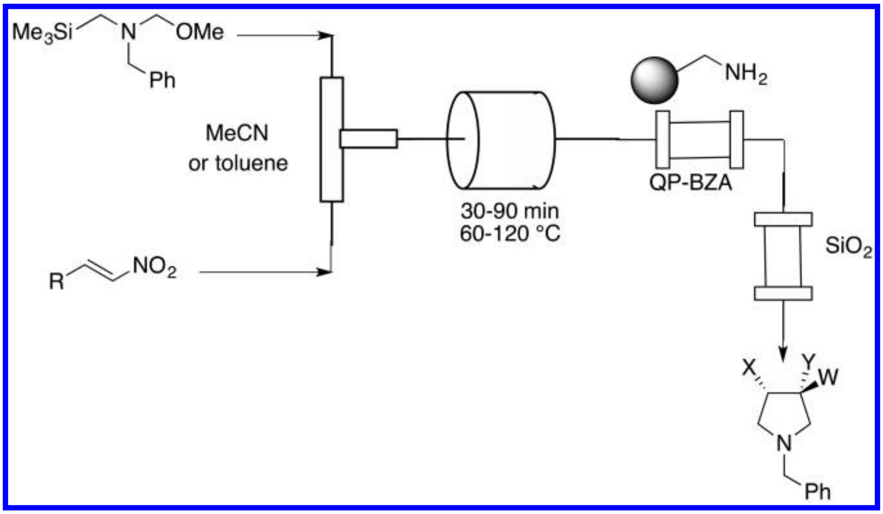
Azomethines are reactive intermediates that can offer many barriers for large-scale usage in a batch reaction. These issues can be minimized by the use of flow.

An unstabilized azomethine undergoes [3+2] dipolar cycloadditions with electron deficient alkenes (Scheme 31). The potentially hazardous reaction can be reduced by use of a flow system to minimize the volume of azomethine at any one time (*114*, *115*).



Scheme 31. Dipolar cycloaddition with azomethines.

For a specific example of Scheme 31, the use of a nitroalkene as the other reactant allows for 3-nitropyrrolidines to be prepared (Scheme 32). The approach used immobilized scavengers (*116*).



Scheme 32. Preparation of 3-nitropyrrolidines.

Azomethines provide a very useful method to access pyrrolidine ring systems. The problems in scaling up in batch mode, due to competing side reactions, makes flow a useful technique for their use in synthesis. However, preparing the precursors is often not cheap and this will hinder growth.

Hydrogen Cyanide

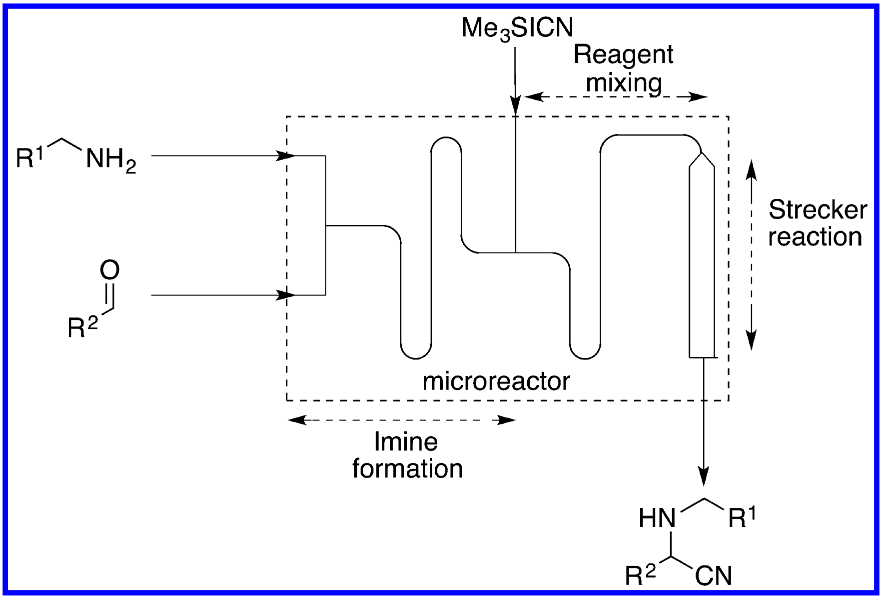
There are several considerable safety issues associated with the use of hydrogen cyanide. Alternatives such as trimethylsilyl cyanide have been proposed to decrease the hazard associated with the volatility of HCN, however, these alternatives still have safety problems associated with them. To circumvent the reactions of metal cyanides with acids, a flow process can be used to thermolyse formamide in the presence of a solid catalyst. The catalyst is kept in suspension by both being finely divided and the movement of gases in the reactor. The reaction involves the thermolytic dissociation of the formamide and capture of the water by the catalyst (*117*).

The conversion of carboxylic acids to nitriles at high temperature has been carried out using a flow reactor (*118*).

Acrylic nitrile is formed by reaction of acetylene with HCN. The reaction is performed in the gaseous phase as a flow process. This minimizes the formation of side products and aids in product separation (*119*).

The Ritter reaction is used to transform a nitrile into an *N*-alkyl amide using an alkene or an alcohol in the presence of a strong acid. Vigorous conditions are required to generate a carbocation from the alkene or the alcohol and the strong acid (*120*, *121*). The reaction has been used in a multistep sequence to prepare 2-aminoadamantane-2-carboxylic acid (See Scheme 52; Grignards section) (*122*).

The Strecker synthesis uses the reaction of aldehydes or ketones with NH_4Cl in the presence of KCN to produce α-amino acids. The initial step is the formation of an imine prior to the addition of the cyanide to provide α-aminonitriles. These intermediates are subsequently hydrolyzed to provide the corresponding α-amino acids (*123–125*). The Strecker reaction has been performed in a flow regime using a solid supported catalyst (Scheme 33). The use of a gallium catalyst has been shown to increase efficiency (*126*). Use of a titanium catalyst allows an asymmetric reaction (*127*).



Scheme 33. Schematic depiction of Strecker reaction in flow.

Hydrogen cyanide and its close derivatives provide methodologies that have seen applications in synthesis, such as the preparation of cyanohydrins and the Strecker reaction. With flow providing a contained system, there will probably not be a great increase in the number of methods and applications, but there could be a move from batch to flow so the cheaper HCN can be used rather than one of the more expensive analogs, particularly when cost becomes a factor such at multikilogram scale.

Unsaturated Sulfur Compounds

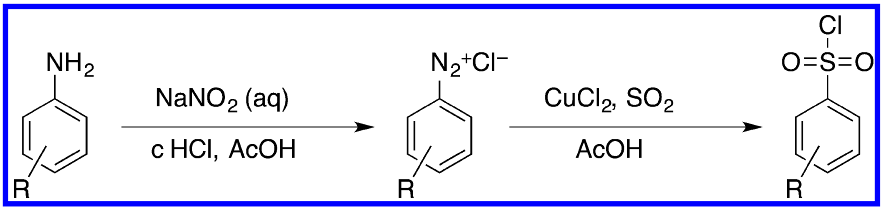
Sulfur compounds, especially volatile ones, such as mercaptans and thioethers, are malodorous; however, the compounds are usually not inherently unsafe. The use of a flow system can help in containing the objectionable odors. Their oxides and some of their derivatives have some safety hazards associated with them and there is a movement towards flow to carry out reactions with these compounds. Some reactions involving these compounds have been used on commercial scale for many years in continuous manner.

Sulfur Dioxide

Sulfur dioxide is a good solvent as well as reagent. Most of the reactions in flow involving sulfur dioxide are carried out to prepare commercial scale products. The major one is the oxidation to SO_3 and the production of sulfuric acid (*128*, *129*). One of the uses of SO_2 is to remove NO_x from emissions, which is are obnoxious gases in their own right.

Techniques have been developed to avoid the use of gaseous sulfur dioxide such as the charge complex with DABCO, which can then be reacted with Grignard reagents to form the corresponding sulfinates (*130*).

A reaction that has been performed in flow is the preparation of sulfinyl chlorides from diazonium salts and SO_2 (Scheme 34). This method allows the use of pressurized gas (*23*), which can require specialized equipment in batch reactions.



Scheme 34. Sulfinyl chlorides from amines.

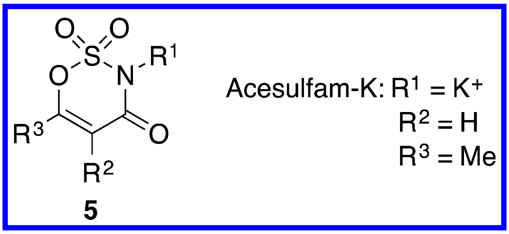
As there are not many methods that rely on the use of sulfur dioxide, flow reactions should not have a great impact on its application in synthesis.

Sulfur Trioxide

This corrosive gas has already found significant use in commercial continuous processes for the production of sulfuric acid. It is made by the oxidation of sulfur dioxide (*128*, *131*).

Sulfur trioxide has been used in flow as a sulfonating agent for aromatic compounds when very good mixing was required to avoid side reactions (*132*).

It is a reagent in some reactions, such as in the production of the artificial sweetener, acesulfam-K. A flow method has now developed for the synthesis of this compound (*133*, *134*). A similar reaction can be used to make other heterocycles with the same backbone **5** (*135*).



5

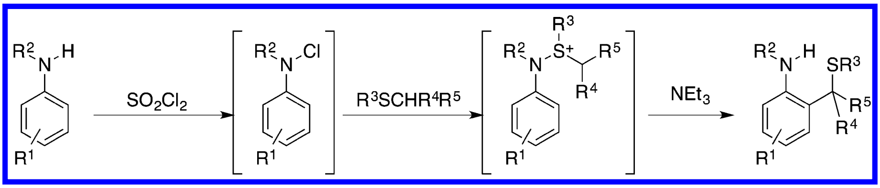
As there are not many methods that rely on the use of sulfur trioxide, flow reactions should not have a great impact on its future application in synthesis.

Sulfuryl Chloride

This is a hazardous liquid that has been used as a chlorinating agent. Many of these reactions involve radical chemistry. As it hydrolyses, it readily evolves HCl gas when in contact with air.

Its main use in synthetic chemistry is to introduce a chlorine atom by a radical reaction using an initiator or light. The process can be performed in a flow reactor with control of the reaction rate by the temperature. An example is provided by the conversion of 2-chloro-5-methylpyridine and converting it to 2-chloro-5-chloromethylpyridine (*136*).

In an approach for the synthesis of an aniline agrochemical was converted to the *N*-chloro derivative with SO_2Cl_2, which was then reacted with a thioether to give the *ortho*-substituted α-thioalkyl substituted aniline after rearrangement (Scheme 35).



Scheme 35. Preparation of an ortho-thioalkyl substituted aniline.

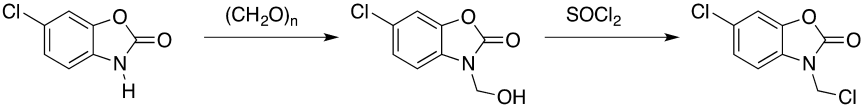
Sulfuryl chloride has limited application in batch chemistry. However, it is useful as a source of chlorine radicals, which makes it a good fit for flow photochemistry. A by-product gas is formed during the reaction, which makes application in flow a somewhat more difficult.

Thionyl Chloride

This reactive liquid has proven very useful for the conversion of hydroxyl groups to chlorides. The reaction produces sulfur dioxide and HCl, the latter sometimes is removed by base. The chlorination is by an ionic mechanism unlike sulfuryl chloride.

The production of off-gases makes applications in flow a challenge. However, there are examples in continuous processing as with the formation of an α,β-unsaturated carboxylic acid chloride prepared from the corresponding acid (*137*).

The containment of a flow system provided a means of preparing a chloromethyl heterocycle, which was then further reacted. The heterocycle was added to a mixture of DMF, paraformaldehyde (see Formaldehyde section for flow examples) and thionyl chloride (Scheme 36) (*138*).



Scheme 36. Preparation of an α-N-chloromethyl heterocycle.

Thionyl chloride will bring about a Beckmann rearrangement of an oxime to form an amide. The use of flow makes this a much cleaner reactions, as side reactions are reduced (*139*, *140*).

Thionyl chloride has wide applicability in batch chemistry, mainly for the preparation of alkyl and acyl chlorides. However, a by-product gas or gases are formed during the reaction, which makes application in flow somewhat more difficult due to pressure build up and gas evolution once pressure is released. Growth would not seem to be anticipated with this reagent but more examples will probably be seen.

Halogens

All of the halogens have safety issues. Keeping the inventory as small as possible alleviates some concerns. Elemental fluorine and chlorine are extremely corrosive and can raise their own safety issues, such as material of construction of the apparatus. This problem is also seen in flow reactions. Bromides, iodides and chlorides are often precursors to organometallic species, such as Grignard and organolithium reagents.

Fluorinations

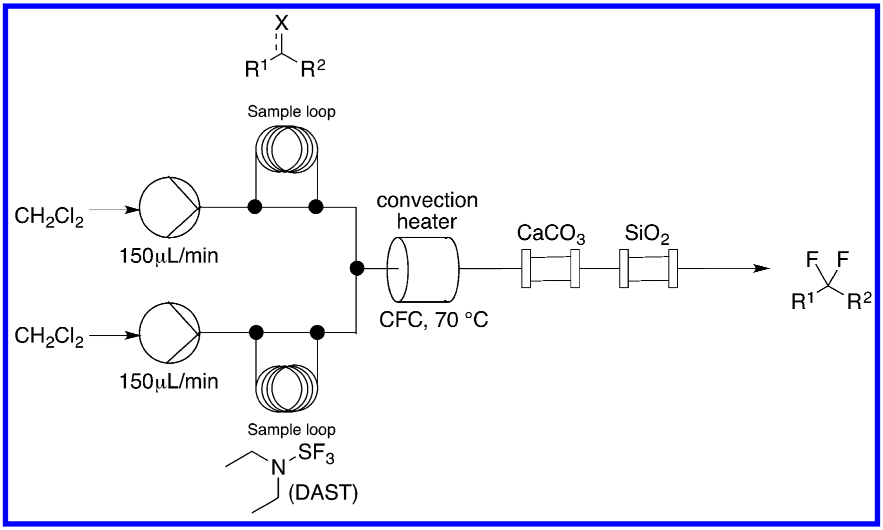
Fluorine is highly corrosive and most fluorinated compounds are obtained from commercially available fluorinated compounds that are produced at scale. This often results in long reaction sequences when these commercial compounds are adapted into a synthesis as flexibility is truncated when a limited subset of fluorinated compounds must do for starting materials.

The use of flow reactions is beginning to make fluoro compounds more accessible, especially if the relatively cheap fluorine gas is employed. Safety issues still have to be considered and the precautions required for manipulating fluorine gas can become complex and expensive (*141–144*).

In some cases the fluoride ion can be used to displace a leaving group; this has been performed in a flow reactor (*145*).

Fluorination of a 1,3-dicarbonyl compound was achieved in flow. The main parameters, optimized were the solvent and the metal catalyst. Fluorine was used as the fluorinating agent (*146*). Aryl fluorides can be prepared from other aryl halides, such as iodide, by Grignard formation followed by a fluorinating agent such as *N*-fluorosultam or *N*-fluorobenzenesulfonimide (NFSI) (*147*), DAST, Ruppert's reagent and Selectfluor (*148*). This seems rather a circuitous route to put in a fluorine but better means are constantly appearing.

Deoxofluor [bis(methoxyethylaminosulfurtrifluoride] has been used under flow conditions to fluorinate steroids (*149*). Diethylaminosulfur trifluoride (DAST) has been used to fluorinate carbonyl compounds and alcohols producing the di- and monofluoro products respectively (Scheme 37). With an acid chloride as substrate and 1 equivalent of DAST, the acyl fluoride was product while 3 equivalents of DAST gave the trifluoro product (*148*). These approaches allow for more flexibility to make aryl fluorides of particular substitution but the use of a fluorination agent renders them more expensive than the use of fluorine gas.



Scheme 37. Route to fluorine compounds.

Another route to aryl fluorides is the reaction of a 1,3-diene with chlorotrifluoroethene (CTFE), followed by base. High temperatures were required so a flow system was employed (*150*).

Reaction of fluorine, diketone and hydrazine in a continuous process provides 4-fluoropyrazoles (*151*).

The incorporation of a fluorine radiolabel into diagnostic agents lends itself to rapid flow reactions (*152*). The half-life of ^{18}F is very short, about 20 minutes, thus flow systems that incorporate more than one operation are good means to make these ephemeral molecules.

With the dramatic increase in biologically active molecules incorporating fluorine in well-defined patterns, this is a growth area whether it is in batch or flow.

However, there is still a need for cheap and safe fluorinating agents, as fluorine gas and fluoride ion are sometimes the best choices. A cheap equivalent to F^+ is still elusive. As fluorine is a corrosive gas, even to glass, materials of construction are important. A flow plant is much cheaper to build than a traditional batch one.

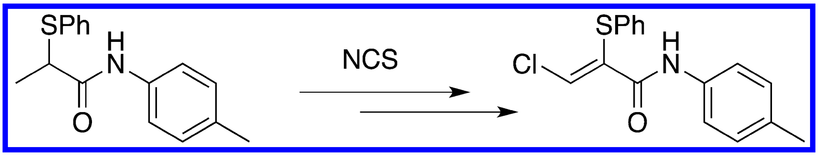
Chlorinations

As for brominations, one of the problems associated with chlorinations is the formation of chlorides as a by-products. There are alternatives. Primary alcohols can be converted to the corresponding chlorides by an uncatalyzed chlorodehydroxylation of the alcohol; the use of flow techniques was necessary to achieve high temperatures and pressures (*153*).

In some cases, over chlorination can be a problem. For the preparation of monochloroacetic acid, this problem was solved by the use of a bubble column reactor and reactive distillation (*154*). A flow system has been used to convert alkanes to alkyl chlorides and then alcohols (*155*).

Chlorinated compounds are also available from diazonium compounds by employing monolithic microfluidic reactors (*24*).

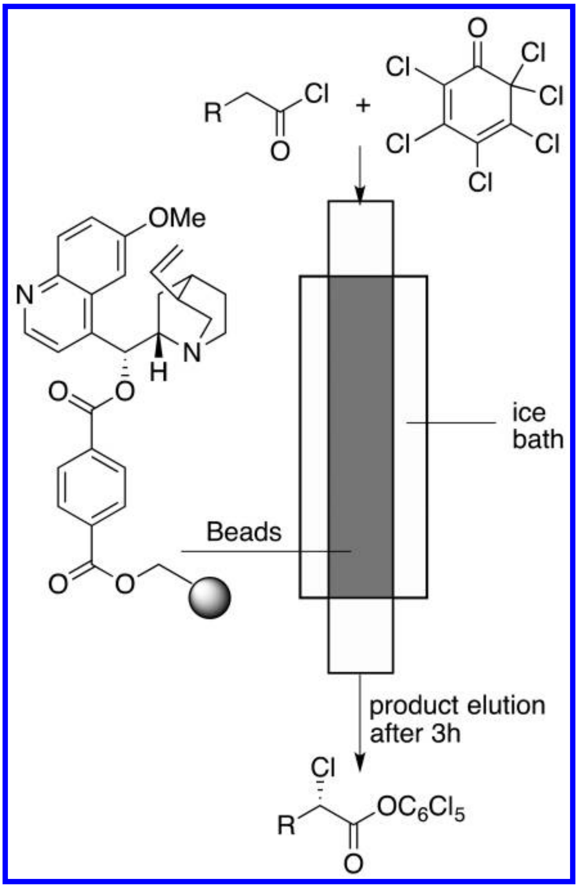
Introduction of chlorine using chlorine gas is often achieved by a radical reaction. To make the process more laboratory friendly, many chlorinating agents have been developed that can follow a radical or ionic mechanism. One such reagent is *N*-chlorosuccinimide (NCS). NCS can be used to convert α-thioamides to α-thio-β-chloroacrylamides in a cascade sequence (Scheme 38). Flow IR and NMR were used to monitor the reaction (*156*).



Scheme 38. Cascade reaction to prepare α-thio-β-chloroacrylamides.

The use of an immobilized asymmetric catalyst provides a method to make chiral α-chloroesters (Scheme 39). The reaction takes place in a column filled with beads (*157*).

Chlorine is a useful reagent that has a number of applications. The use of a flow photoreactor can reduce many of the problems seen when this methodology is used in batch. Growth in this area could be faster with flow, as it alleviates some of the risks and chlorine can be used directly rather than a chlorine delivering agent.



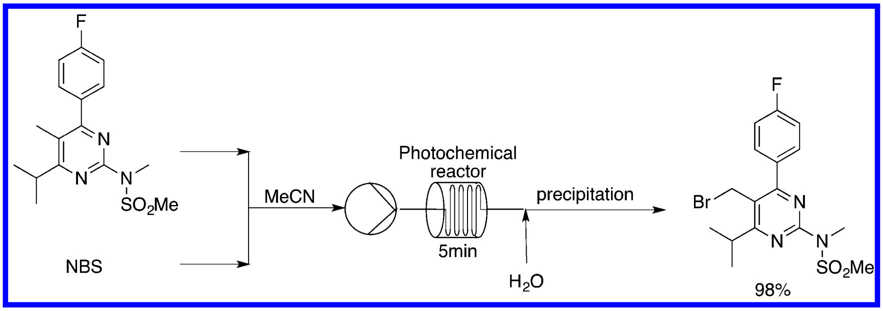
Scheme 39. Preparation of chiral α-chloro esters from acid chlorides.

Brominations

There are many methods to introduce bromine into a compound, especially for aromatic, allylic, benzylic and carbonyl compounds. Many of these methods result in the formation of corrosive hydrogen bromide, which is a safety hazard and must be disposed of or recycled. This is not in line with the principles of green chemistry (*158*).

Efforts have been made to avoid the use of bromine itself. One example is the use of ammonium bromide in the presence of oxone®, which has been run in flow. The method allows for the monobromination of arylalkyl, cyclic, acyclic 1,3-diketones and β-keto esters. α,α-Dibromination can be achieved by use of more reagents (*159*). Other brominating reagents have found widespread usage in batch chemistry rather than flow, such as *N*-bromosuccinimide (NBS).

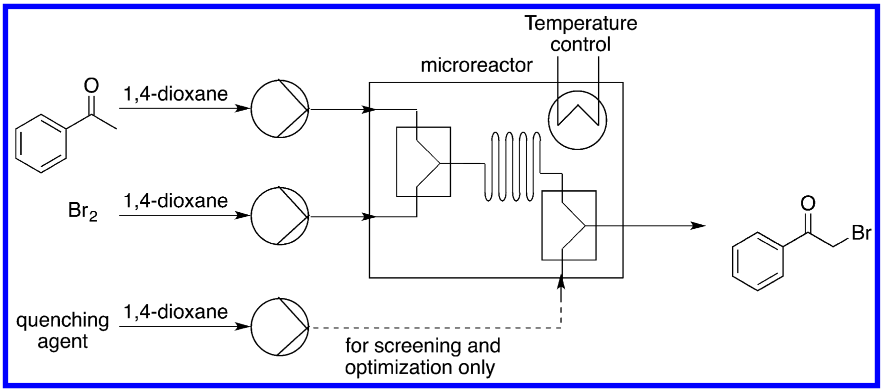
As mentioned above, some brominations are achieved by the use of a radical reaction, initiated by light. Unfortunately, this approach can lead to runaway reactions (*160*). The use of a flow system alleviates some of the safety problems. The formation of HBr as a by-product can be circumvented by the use of NBS as the bromine source (*41*, *161*). This is highlighted by an approach to an intermediate for rosuvastatin (Scheme 40) (*162*).



Scheme 40. Preparation of an intermediate for rosuvastin by a photochemical bromination.

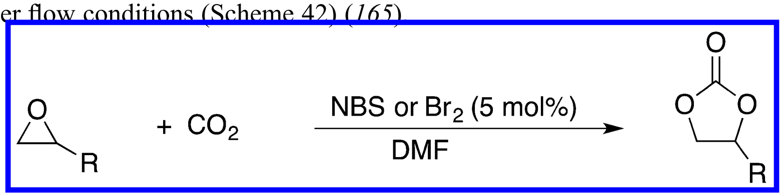
The use of a visible light reactor, in the presence of [Ru(bpy)$_3$Cl$_2$], with carbon tetrabromide as the bromine source, provides a high yielding method for the conversion of secondary alcohols to the corresponding bromides (*163*).

The α-bromination of a carbonyl compound follows an ionic mechanism and forms a stoichiometric amount of HBr, as only one of the bromine atoms from Br$_2$ is incorporated into the product. The method can suffer from autocatalysis in batch mode and polybrominated products can be formed. The mono α-bromination of acetophenone was successfully preformed in a flow reactor using optimized reaction conditions to control the autocatalytic behavior (Scheme 41) (*164*).



Scheme 41. Bromination of acetophenone.

As a related reaction, some reactions require only catalytic amounts of bromine (or NBS), such as the preparation of cyclic carbonates from epoxides under flow conditions (Scheme 42) (*165*).



Scheme 42. Conversion of an epoxide into a cyclic carbonate.

The introduction of bromine atom into a molecule provides a number of subsequent transformations to become available, such as the formation of an organometallic reagent or displacement by a nucleophile. It is a liquid but with a high vapor pressure and highly corrosive. This has led to the development of alternative brominating agents, which are less hazardous. However, the use of flow can circumvent many of these problems, permitting elemental bromine to retain a place in synthetic chemistry and a steady growth in the number of applications will probably continue.

Iodinations

Iodine is a solid that tends to sublime which renders handling it problematic. For instance, it can sublime up a reaction vessel to undesired locations. Its use has few distinct safety issues but flow is beginning to be used for the preparation of iodo compounds, especially as this can be coupled with subsequent reactions to make use of the highly active halogen. The safety issues associated with the use of hypervalent iodine compounds often used synthetically makes these good candidates for use in a flow system.

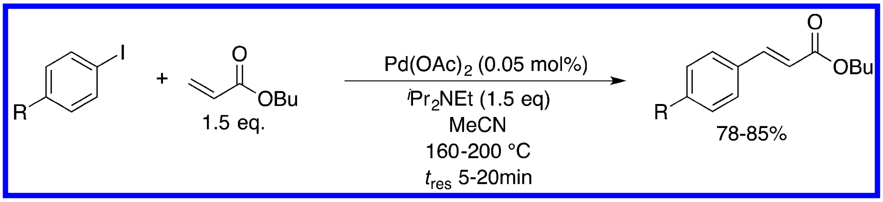
As with its sister halogens, alternative reagents have been developed to replace iodine. The preparation of *N*-iodomorpholinium hydroiodide, a fine solid and iodinating agent was performed in a flow system illustrating that solids can be handled (*166*).

Aryl iodides can be prepared in high yield in a continuous process, the success was attributed to a high speed mixer (*167*, *168*).

Iodine has also been used to prepare helicenes by cyclizations. These reactions involve a photolysis with an organometallic sensitizer; a flow approach reduces the reaction time (*169*).

Iodo azide, a highly explosive compound, has been used to prepare azides and the product can be taken on for further reaction (See Azides) (*72*).

Aryl iodides are used in a wealth of reactions that can be performed under flow conditions, such as the formation of Grignards and organolithium derivatives (*170*). They can also be used in aryl coupling reactions where low-loadings of the metal catalyst can be easily achieved in flow. Safety is increased as a low boiling solvent, such as acetonitrile, can be used at high temperatures (Scheme 43) (*171*), while more traditional approaches used high boiling solvents, such as NMP and DMF, that are regulated solvents (*172*).



Scheme 43. Use of an aryl iodide in a coupling reaction.

Iodine is a solid and does not have many of the problems associated with the use of the other halogens. However, hypervalent iodine compounds can be explosive and this problem can be minimized by the employment of flow technology. Certainly within a laboratory setting, the use of hypervalent iodine should grow. For larger scale applications, these agents will need to be made in flow and then used immediately.

Organolithium and Grignard Reagents

As many of these compounds are made from organohalides, this section has been included here after halogenations. Only reagents that are widely used in organic synthesis are discussed, namely organolithiums and Grignard reagents.

Organolithiums

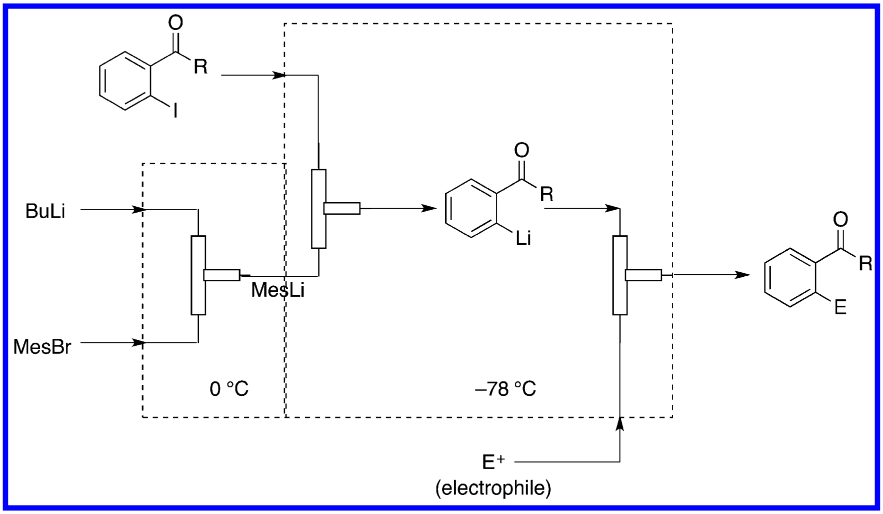
Organolithiums are reactive compounds that offer a wide range of synthetic methodologies. The most common methods of preparation are by halogen lithium exchange or deprotonation with another organolithium compound. In batch mode, low temperatures are often used to minimize side reactions. These arise due to the presence of excess substrate at the beginning of a reaction or the presence of the by-product organohalide formed by the lithium-halogen metallation. In some cases, the side reactions can give rise to other reactive species, such as elimination of an adjacent aryl halide to form a benzyne (*173*). In a smaller number of cases, the intermediate may be thermally unstable.

As the reactions are rapid, and the stoichiometry can be carefully controlled, organolithiums are good candidates for flow reactions See Organolithium Chapter). This can avoid the use of very low temperatures and minimize side reactions. The fast reaction times allow for transformations that would be impossible in batch-mode. An advantage of flow is that it can move the freshly formed desired product downstream before it can react with substrate that is being added.

An organolithium can be generated by halogen-lithium exchange (*174–177*). Vinyllithium can be generated by bromine-lithium exchange with one equivalent of *sec*-butyllithium at 0° to 20°C (*178*).

However, one area that still needs to be addressed is when a solid is formed in the reaction, such as a lithium halide byproduct from an alkylation or insoluble lithium alkoxides (*8*). Several methods, such as oscillating reactors and the use of ultrasound show signs of promise to avoid plugging the reactors during flow reactions (*8*).

The use of flow methodology allows reactions to be performed, which would be very difficult in batch mode due to the instability of the intermediate. An example is provided by the formation of an aryllithium in the presence of a carbonyl group within the same molecule (Scheme 44) (*179–181*).

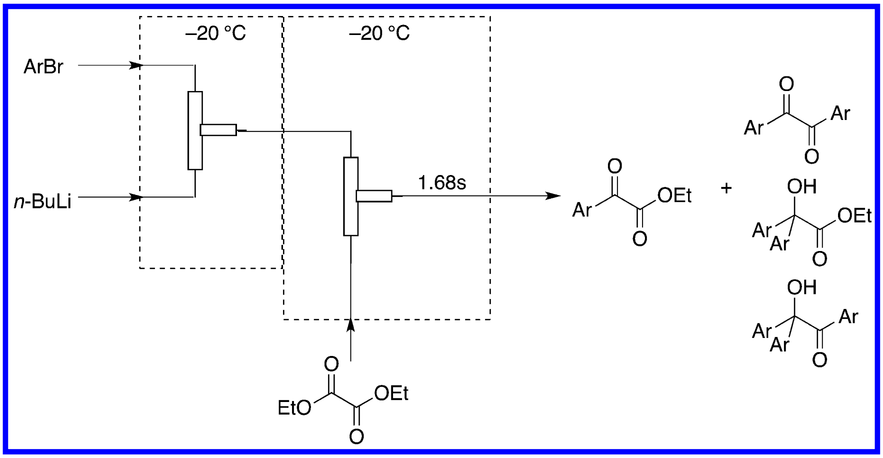


Scheme 44. Preparation and reaction of a carbonyl-containing aryllithium.

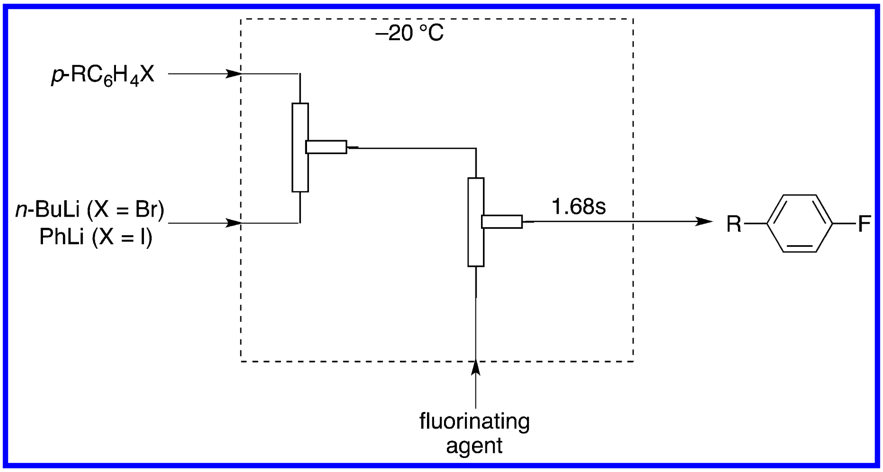
Asymmetric organolithium derivatives can sometimes be prone to racemerize and flow can be used to minimize loss of stereochemistry (*182*).

Flow can also stop over-reaction as illustrated by the reaction of an aryllithium with diethyl oxalate (Scheme 45). The major product is the ketoester (*183*). Reaction of an organolithium with an ester can provide the ketone without the frequent problem of further reaction to the tertiary alcohol (*184*).

Aryllithiums can be used to prepare aryl fluorines (see also Fluorine Section) with *N*-fluorodi(benzenesulfonyl)amine (NFSI) or *N*-fluorosultam as the fluorinating agent (Scheme 46) (*147*).



Scheme 45. Reaction of an alkyllithium with diethyl oxalate.

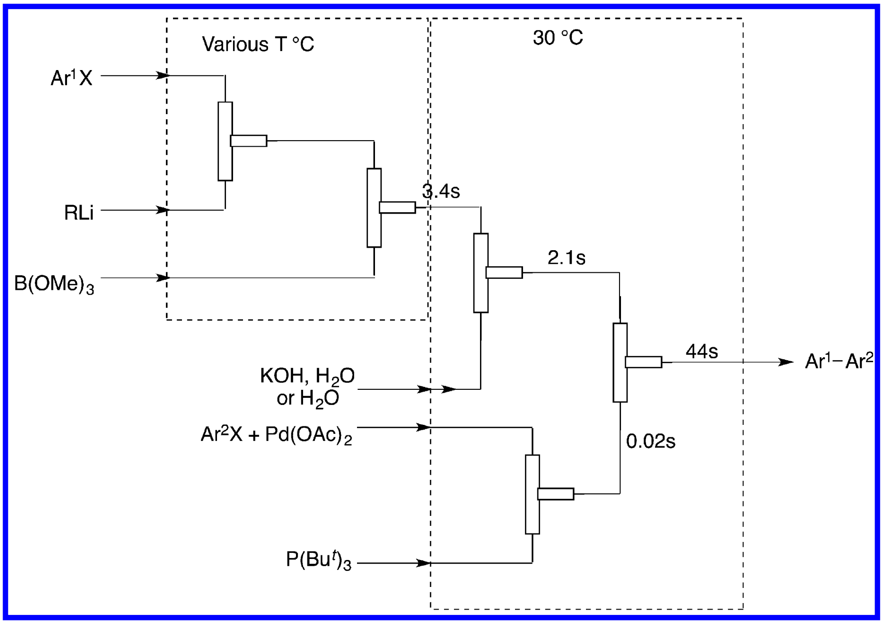


Scheme 46. Fluorination of an aryllithium.

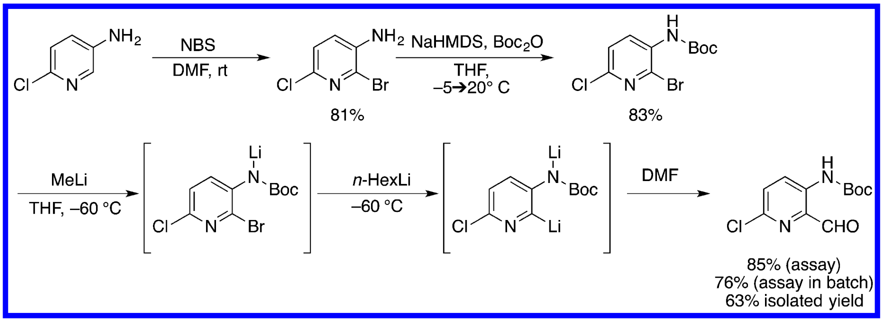
Palladium catalysis can be used to effect a coupling between an aryllithium and an aryl halide (*185*). An alternative catalyst is iron(III) chloride (*186*).

In perhaps a more traditional approach to biaryl compounds, boron can be introduced following formation of an organolithium (*187*). A subsequent Suzuki reaction can also be performed in flow (Scheme 47) (*188*).

Formylations of organolithium compounds can be very useful transformations. In the synthesis of an intermediate of an Akt kinase inhibitor, flow produced higher yields than the corresponding batch process (Scheme 48) (*189*). The formylating agent in this example was DMF.



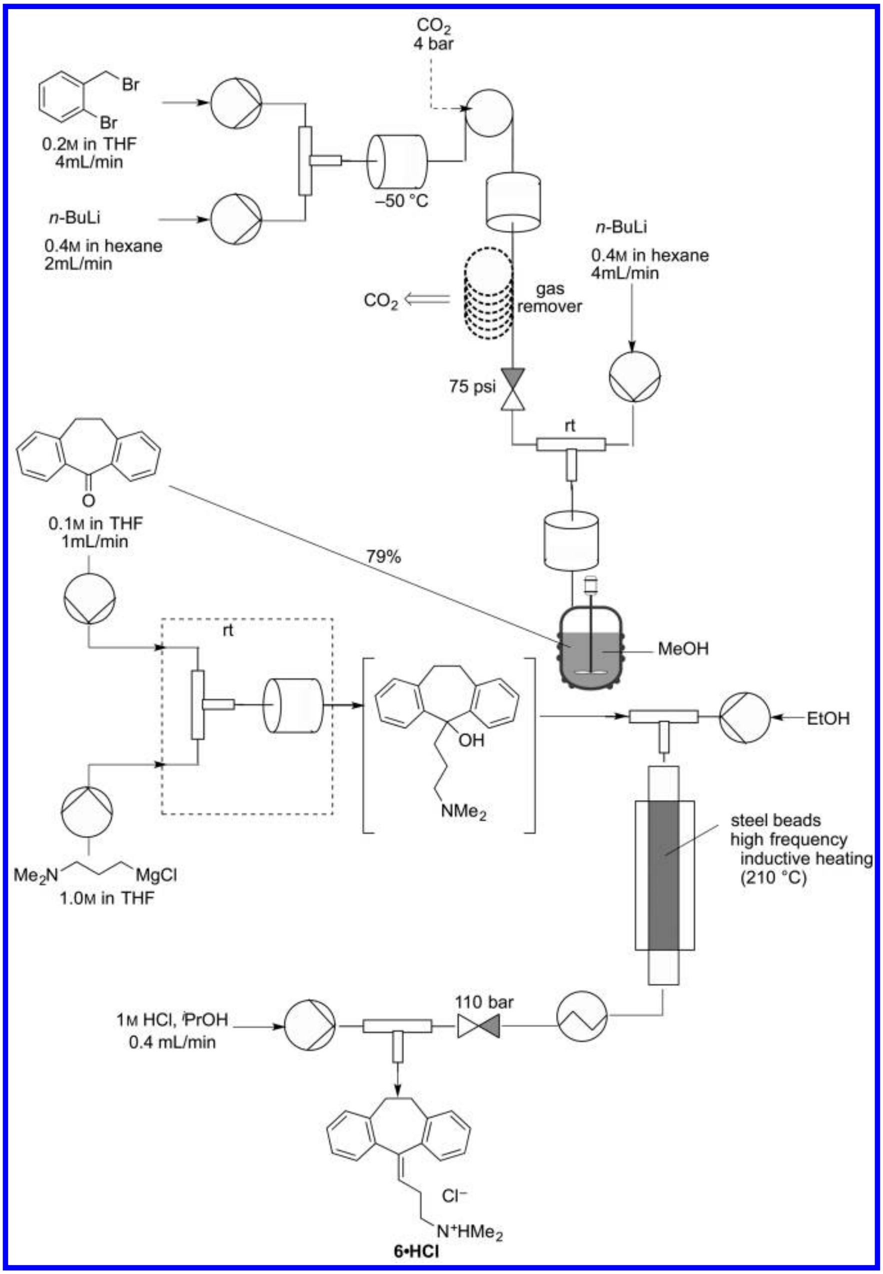
Scheme 47. Boronation of an aryllithium followed by a Suzuki reaction.



Scheme 48. Formylation of an arylithium.

Sometimes the use of a flow method can help with work-up procedures if the product is unstable as air and moisture can be excluded. In addition, the time needed to perform the work-up can be much faster in flow, as it is continuous. This approach was used in a preparation of 4,4,5,5-tetramethyl-2-(3-trimethylsilyl-2-propynyl)-1,3,2-dioxaborolane, a propargylation reagent (*190*).

As a final example, a multistep sequence to amitriptyline (**6**) illustrates the use of both an organolithium and a Grignard reagent in flow (Scheme 49) (*191*). A Wurtz coupling is performed with an organolithium. Another organolithium intermediate is also used to introduce carbon dioxide into the molecule using the tube-in-tube technique. A Grignard addition with a carbonyl group is used to introduce the final part of the molecule (see also Grignard Section)



*Scheme 49. Synthesis of amitriptyline (**6**).*

As organolithium compounds are air and moisture sensitive and some are pyrophoric, they have to be handed in closed systems. The generation of an organolithium compound can be very fast concluding in fractions of a second. Thus the use of flow allows the removal of the reaction mass from the input points to prevent the undesired reactions of excess reagents with the product. Flow also allows for the quick generation and reaction of "unstable" organolithium compounds. This technology has grown in popularity to provide possibilities that are impossible in batch reactions. We expect flow techniques to continue to expand for this chemistry. The problem of solids formation and plugging, however, is still an issue.

Grignard Reagents

These reactive intermediates can be used in a flow regime. Metallic magnesium can be used for their generation (*192*, *193*). The metal approach has been used to continuously prepare vinyl Grignards (*194*). An alternative is to use a halogen-metal exchange reaction where a preformed Grignard, such is *iso*propylmagnesium halide, reacts with an organic halide in an analogous manner seen for organolithium compounds when prepared from an organic halide. The formation of Grignard reagents in flow can be monitored conveniently by in-line IR (*170*, *195*). NMR has also been employed to monitor the reaction (*196*).

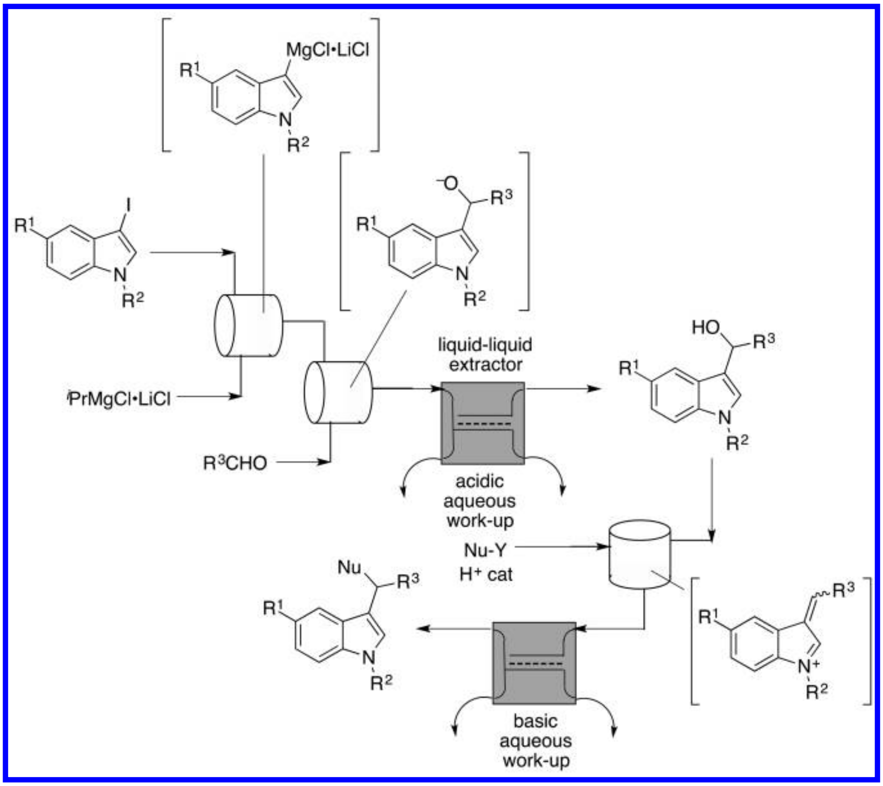
In a manner similar to organolithiums, aryl Grignard reagents can be coupled to aryl halides in the presence of a nickel catalyst (*197*).

As with batch reactions, a Barbier reaction can be used in flow to lessen environmental impact (*198*).

Reaction of the Grignard reagent with carbon dioxide to give a carboxylic acid in flow with a gas-permeable membrane reactor provides a simple process that can be monitored by IR (*199*).

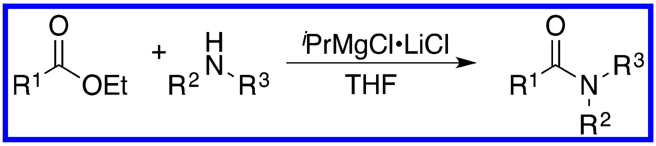
As with batch methods, Grignard reagents react with carbonyl compounds to provide the corresponding alcohols (*200–202*). This approach has been used to prepare 3-hydroxymethylindoles (Scheme 50) (*203*).

Grignard reagents can be reacted with various unsaturated molecules containing heteroatoms (*204*). In an early example of a flow reaction, Grignard reagents were reacted with fluoroacetonitrile. The reaction was used to prepare 2-amino-2-fluoromethyl-3-pentenentrile This compound was utilized as an intermediate in the preparation of an inhibitor of ornithine decarboxylase (*205*). The addition to a nitrile followed by hydrolysis gives useful method to prepare ketones (*206*).



Scheme 50. Preparation of 3-hydroxymethylindoles.

The use of a Grignard reaction in flow allow the use of an ester as an acylating agent for amines (Scheme 51) (*207*).

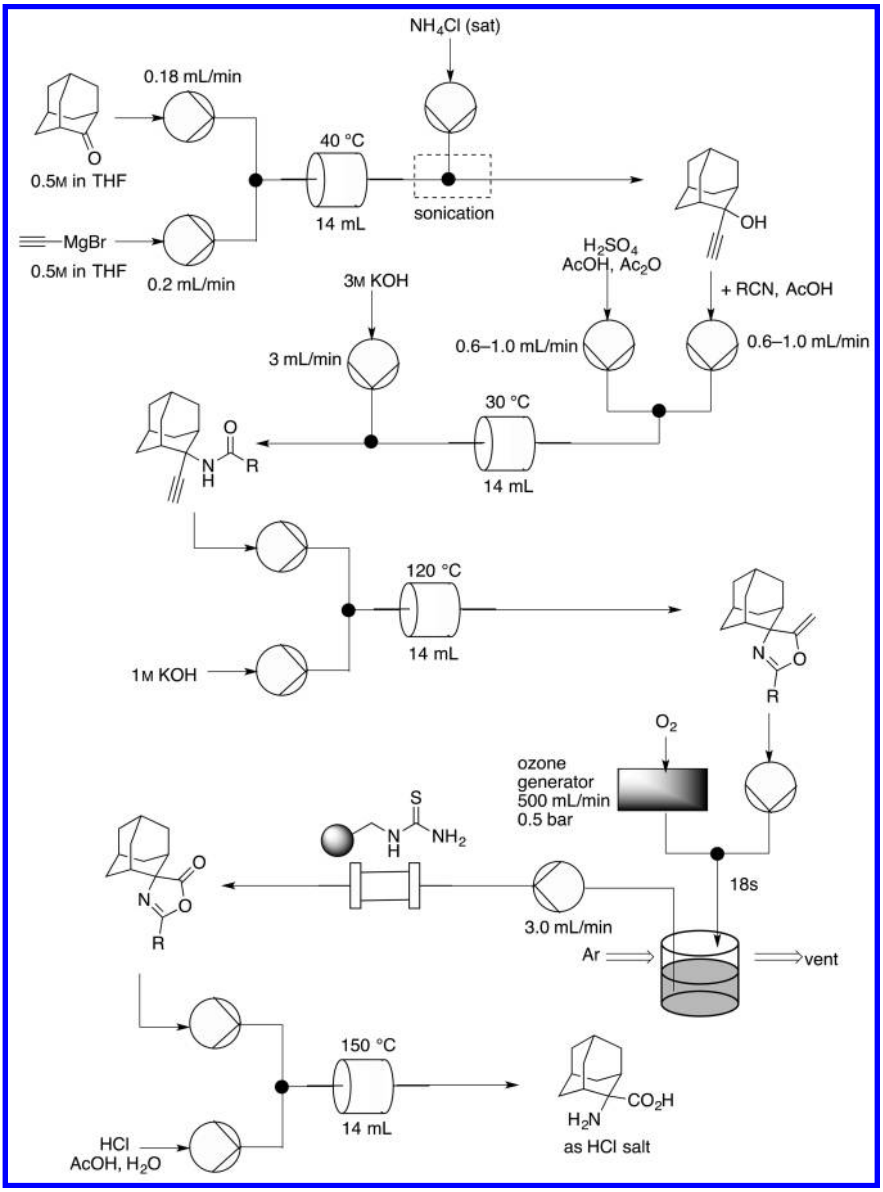


Scheme 51. Use of an ester as an acylating agent with a Grignard reagent.

A flow approach allows an aryl Grignard reagent to react with an α-halo ester to produce the α-aryl ester (*208*).

Boron electrophiles are also possible (*209*, *210*).

An example of the use of a Grignard reagent in a multistep sequence is the synthesis of amitriptyline (**6**). This sequence of reactions also includes the use of an organolithium compound (see Organolithiums; Scheme 49) (*191*). Another example is the synthesis of 2-aminoadamtane-2-carboxylic acid. In addition to a flow Grignard reaction, a Ritter reaction and ozonolysis are also used (Scheme 52) (*122*).



Scheme 52. Preparation of 2-aminoadamtane-2-carboxylic acid.

Grignard reagents can be prepared from an organohalide and magnesium metal. This preparation approach presents the problem of requiring initiation. Additionally, as the reaction progresses the metal particles become very small towards the end of the reaction, and that may lead to plugging. The delayed initiation problem has a number of solutions developed from batch mode technology including the use of preformed Grignard reagent, the use of part of a previous Grignard formation to act as initiator, or by the addition of a commercially available agent. One of the solutions for flow reactions is to use two feed containers for the metal stream, so they can be exchanged during the reaction. The smaller metal particles can call blockages and this needs to be addressed by filters.

Unsaturated Oxygen Compounds

Carbon Dioxide

Carbon dioxide is introduced into a flow reaction as a gas, often through the tube-in-tube methodology. Examples are found in other sections. It is useful for the preparation of carboxylic acids from organometallic reagents.

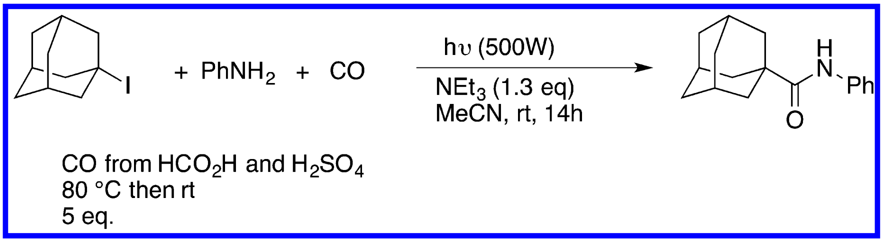
Carbonylations

Carbonylations are performed as continuous processes on large scale. For smaller scale reactions, there has been less activity as compared to other reactions. This may be due to the number of alternative means to access an aldehyde using batch reactions. However, one important example that has received much attention is the generation of phosgene (see Phosgene Section).

In addition, there are regiochemical and stereochemical issues with a carbonylation, both of which are still to be satisfactorily solved. Propene hydroformylation can be accomplished by use of a supported aqueous phase Rh-NORBOS catalyst (*211*).

Alkoxycarbonylations or aryl iodides can be achieved using the tube-in-tube technique (*212*).

Amides can be prepared from alkyl iodides, amines and CO by flow carbonylation (Scheme 53). In addition to the more traditional metal catalyzed carbonylation, light can also be used (*213*).



Scheme 53. Formation of amides from alkyl iodides.

Direct conversion of nitrobenzene to phenylisocyanate can be achieved by reaction with CO (*214*).

Carbonylations are often run in continuous processes for large-scale preparations. These can now be scaled down to increase the versatility of this chemistry. However, there is limited application in smaller scale synthesis. Growth, therefore, will probably be slow.

Formaldehyde

This gas has some safety and health issues as well as being difficult to handle. Even in flow reactions, a formylating agent is usually used to introduce the formyl group, even though some of them have their own issues, such as *N,N*-dimethylformamide (DMF) and Vilsmeier reagents (see sections on Alkyllithiums and Vilsmeier reagents).

The stable forms of formaldehyde (anhydrous) are the trimer trioxane and the polymer, paraformaldehyde. Heating of either one gives the monomeric species, but this can quickly repolymerize giving rise to blockages. There are also thermal issues (*215*).

Most of the uses of formaldehyde in flow are high temperature, commercial examples.

The problems associated with the use of this compound still remain in flow. Alternative reagents will, no doubt, continue to be used. Flow, however, does allow the ability to run high temperature reactions so as to put the formaldehyde into the gas phase, but then it must also be used in a subsequent reaction at high temperature.

Phosgene

Although a useful reagent, it goes without saying that phosgene has considerable safety issues. It is simple to make from chlorine and carbon monoxide, which can be performed in flow (*216–220*). To alleviate some of the safety problems, flow reactions have been used to contain the reactive and noxious reagent.

Isocyanates are available from phosgene with an amine in a fluidized bed reactor (*221–225*).

Aryl chloroformates can be accessed from an aromatic hydroxyl compound, phosgene and an organic base (*226*, *227*).

α,β-Unsaturated carboxylic acids can be converted to the acid chlorides with phosgene under flow conditions (*137*).

Examples of the use of phosgene, once it is prepared in flow, are given in other sections. For example. phosgene is useful for the preparation of Vilsmeier reagents (see section on Vilsmeier Section) (*106*, *228*).

Phosgene is usually made using a flow process; the two starting materials CO and Cl_2 both have safety issues themselves. Coupling the formation of phosgene to a subsequent reaction in flow will probably be an area of research leading to a growth in use.

Reductions

Hydrogenation reactions are used in large-scale chemistry. Other reducing agents are mainly based on metals and have issues with by-product formation, as well as reactivity issues.

Metal Hydrides

Although metal salts can be a waste disposal issue, there are some reductions that have been performed in flow with metal hydrides. One such example is a Dibal-H reduction of a nitrile to give an aldehyde (*229*). There are other reductions that are still difficult to perform by hydrogenation, such as the reduction of an amide to an amine.

The use of an X-Cube (*230*) was used in the reductive amination of amines with ammonium formate and Zn dust. This method was superior for carbonyl groups at the benzylic position (see Hydrogenations Section) (*231*).

Flow does not solve the problems associated with the use of a molar amount of the reductant nor reduces the formation of by-products. No doubt, their use will continue when hydrogenations cannot effect the desired transformation. However, some of these are now moving towards hydrogenation, such as the reduction of an amide to an amine without amide bond cleavage.

Hydrogenations

Both flow oxidations and reductions can be performed with heterogeneous catalysts (see also section on Oxidations) (*232*). The use of flow can provide a much smaller equipment footprint, and because of the safety issues of using hydrogen, a much higher throughput for a given volume (*233*). It is also possible to greatly reduce the inventory of hydrogen in the reactor and laboratory.

The ThalesNano H-cube has proved popular for smaller scale operations, as it removes many of the safety issues associated with the use of hydrogen. The equipment is also available in larger sizes (*234*). The equipment is explosion proof, cartridges are used to hold the catalyst and the hydrogen is generated by electrolysis of water (*234–236*). It also allows for the formation of deuterium, rather than hydrogen, by replacement of water by D_2O. A similar system has been used to deuterate a wide range of substrates (*237*, *238*).

The addition of an autosampler to the front end allows a number of reactions to be monitored in a short time period (*234*, *235*, *239*, *240*).

There is a wide range of reductions performed with an H-Cube and using a range of catalysts (*116*, *241–243*). The popularity of the H-Cube and the lack of need for a an external source of hydrogen gas has greatly increased the use of flow hydrogenations, especially in laboratory settings. Undoubtedly, this trend will continue.

Other equipment can also be used, as illustrated by the reductions of nitro groups (see Nitration Section) (*244*), as well as other substrates (*245*).

In addition to cartridges, a catalyst-trap microreactor can be used for heterogeneous hydrogenations (*246*). Scale up can be achieved by scaling out (*247*). Separation of the catalyst from the reaction stream can be a challenge, especially if recycle is required for an economical process. Flow through membranes have also been used to aid with this separation (*248*, *249*).

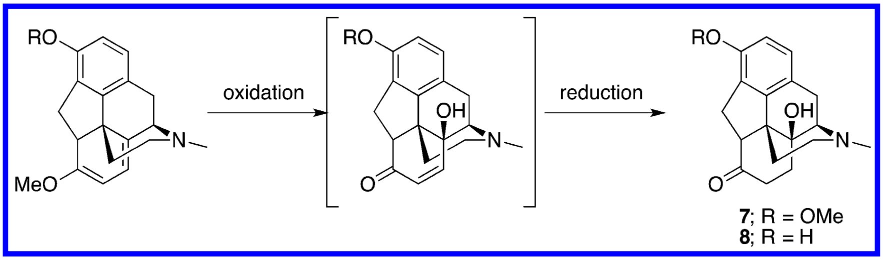
Hydrogen can be introduced into a flow system using the tube-in-tube approach (*250–252*).

The hydrogenation reaction in a flow system can be monitored by NMR using *para*-hydrogen, a spin isomer of hydrogen (*253*).

The choice of metal can have a profound effect on the chemoselectivity of the reduction. For example the use of iron(0) nanoparticles in water under flow conditions reduces alkenes, alkynes, aromatic imines and aldehydes in almost quantitative yields while aldehydes, ketones, esters, arenes, nitro and halogens remain untouched (*254*).

Asymmetric hydrogenations can be performed in flow (*233*, *252*, *255–257*), some using a self-supported chiral catalyst (*258*) where the catalyst immobilizes itself (*259*). A trickle bed reactor has also been used (*260*), as has supercritical CO_2 (*261*, *262*).

Many of the reductions that have been done in batch mode are now available in a flow regime. This includes a dehalogenation (*263*). An immobilized catalyst was used for the hydrogenation of an alkene in a synthesis of oxycodone (**7**) (Scheme 54). The oxidation was achieved in flow as well using a peracid (see Section on H_2O_2). The sequence could also be used for oxymorphone (**8**) synthesis (*264*, *265*).

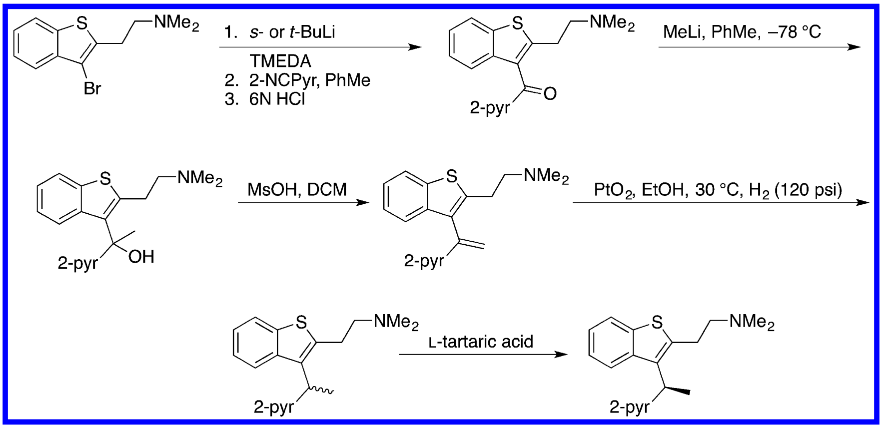


*Scheme 54. Preparation of oxycodone (7) and oxymorphone (**8**).*

There are many reductions of nitro compounds to amines (see Nitrations Section).

The reduction of amides to amines with hydrogen has been elusive, although it can be achieved with a variety of metal hydrides. Use of hydrogen in a flow system has now been shown to effect this transformation making it much greener (*266*).

In a synthesis of NBI-75043, a flow hydrogenation was employed (Scheme 55). The reduction produced significant amounts of the enantiomer and a clean up had to be performed. One of the problematic steps in the synthesis was the reaction of the organolithium with the pyridinyl nitrile (see Organolithium section) (*267*).



Scheme 55. Preparation of NBI-75043.

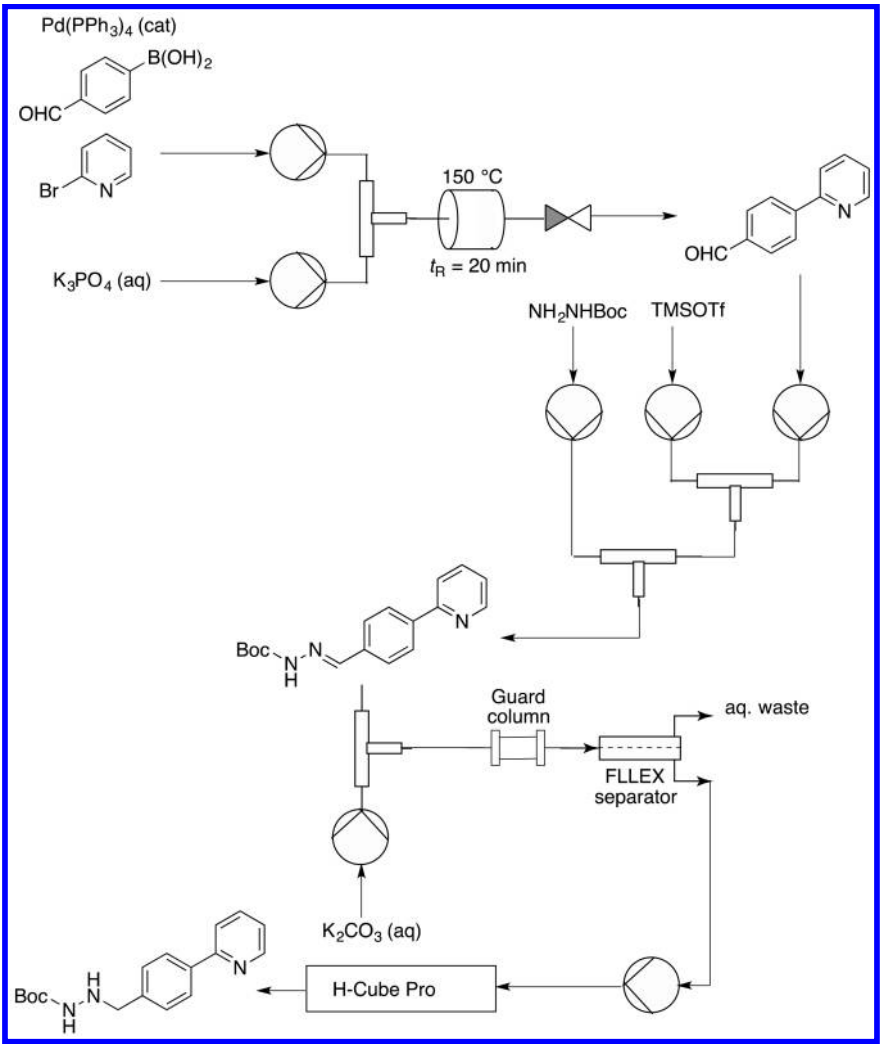
As a metal catalyst is employed, coupling reactions can be performed sequentially after hydrogenation of the product (*44*, *268*). A slight variation on this sequence was used in a flow synthesis of an intermediate for the HIV protease inhibitor atazanavir (Scheme 56) (*269*).

As with batch reactions, transfer hydrogenations can be used in flow to avoid the use of hydrogen gas (*49*, *270*, *271*). The reaction can be asymmetric (*272*). A ThalesNano X-cube (*230*) can also be used for reductions (see Metal Hydrides Section). With 10% Pd–C in the presence of ammonium formate, ketones could be used to produce amines. This method was superior for non-conjugated carbonyl compounds, as opposed to conjugated ones where Zn dust gave better results (*231*).

Hydrogenation is a powerful reaction. The flow equipment is now available to make the reaction available to most laboratories and it can be scaled up. The use of a closed system reduces many of the safety issues; the system is closed and the apparatus is explosion proof. The number of applications will continue to grow, especially as asymmetric versions become widely available.

Oxidations

The need to perform reactions, such as oxidations, in an organic solvent raises many safety issues. However, there are a number of reagents to perform these reactions that have been adapted to flow technology. Oxidations are often considered green methods when no metal catalyst is required and oxidants such as air or hydrogen peroxide are used (*273*).



Scheme 56. Synthesis of an intermediate for atazanavir by flow chemistry.

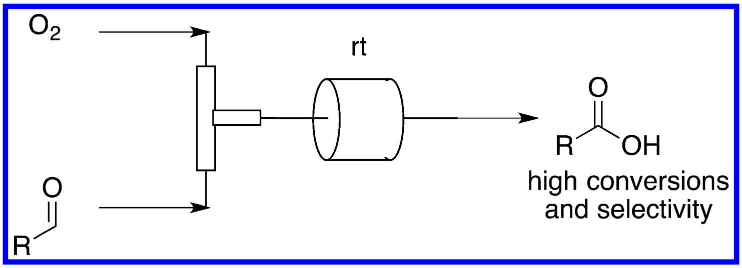
Oxygen

Oxygen is the ultimate oxidant as the only by-product will be water. However, with many organic solvents it has safety issues from producing explosive mixtures as well as providing an excellent source of oxidant if a fire does result.

Oxygen can be introduced by the tube-in-tube method (*274*).

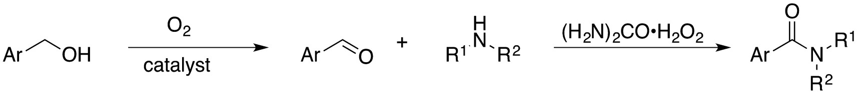
Use of a diluted oxygen source can mitigate some of the safety issues of using this gas to avoid explosive limits of oxygen concentration. In the presence of a palladium catalyst alcohols can be oxidized to the corresponding carbonyl compounds (*275*).

Oxidation of an aliphatic aldehyde to the corresponding carboxylic acid can be accomplished by oxygen without the need to have a catalyst (Scheme 57) (*276*). Diluted oxygen can also be used as the co-oxidant for TEMPO oxidations (*277*).



Scheme 57. Oxidation of an aldehyde in a flow regime.

Reaction of an alcohol and an amine in the presence of oxygen and urea hydrogen peroxide provide the amide in a multistep sequence (Scheme 58). Packed bed catalyst is used to convert the alcohol to aldehyde (*278*).



Scheme 58. Preparation of an amide from an alcohol.

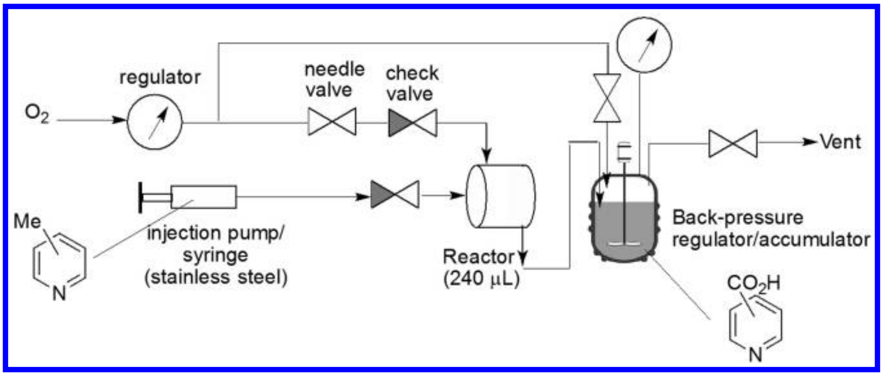
Flow oxidations can be performed with heterogeneous catalysts (*232*). These can be in a fixed bed reactor of monolith columns (*279*).

Oxidation of ethylbenzene can produce acetophenone or benzoic acid by control of the reaction conditions. A $CoBr_2/Mn(OAc)_2$ catalyst was used with air as the source of oxygen.

In a similar manner, lactate can be oxidized to pyruvate in the presence of a vanadium catalyst (*280*).

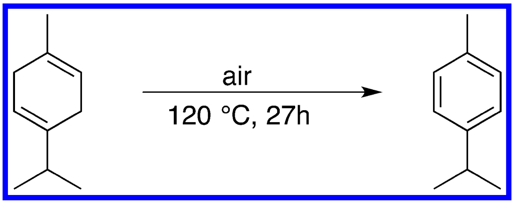
For the oxidation of glucose, a heterogeneous gold catalyst can be used (*281*). Other compounds can be oxidized with different catalysts (*282*). This includes dehydrogenations (*283*).

Oxidation of 2-, 3-, or 4-picoline to the corresponding carboxylic acids occurs in flow with a short reaction time and at moderate temperatures with air (Scheme 59) (*284*). Although shown as a reactor, the back-pressure regulator and accumulator can also contain sample vials.



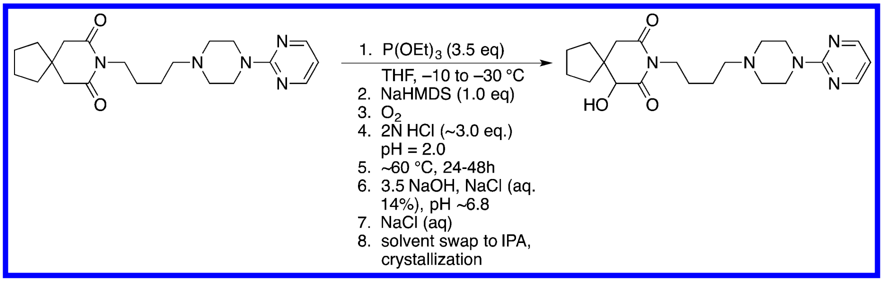
Scheme 59. Oxidations of 2-, 3-, or 4-picoline.

Dehydrogenation of γ-terpinene to *p*-cymene is achieved with oxygen only with no catalyst (Scheme 60). The rate of reaction depends upon the vapor/liquid phase equilibrium and the amount of oxygen in the vapor phase (*285*).



Scheme 60. Conversion of γ-terpinene to p-cymene.

In a synthesis of 6-hydroxybuspirone, the oxygenation of an enolate was required (Scheme 61). The oxidation was achieved using a trickle bed reactor. The oxidation was scaled up by numbering up (*286*, *287*).



Scheme 61. Synthesis of 6-hydroxybuspirone.

Flow has been used to increase mass transfer in biphasic biotransformations that require oxygen (*288*).

Oxygen has been used to prepare acrolein (see Acrolein Section).

Gaseous oxygen has the major disadvantages being part of the triad required for combustion. This is particularly of concern when a flammable organic solvent is used. The use of flow methods allows the mixing of oxygen and the combustible solvent in a flow regime with subsequent reaction that consumes the oxygen. The liquid content of oxygen at the end of the stream can be almost zero. With the move to green chemistry, and the development of catalysts to bring about the desired oxidation, this approach is set up for fairly rapid growth.

Acrolein

This simple molecule is not easy to obtain due to its reactivity and tendency to polymerize. A number of methods have been developed to prepare the molecule so that it can be used immediately. An example is a two-step oxidation of propylene in steam with air; mixing and a flame arrester are used to maintain safety. The yield is 98% (*289*). A catalyst can also be used (*290*, *291*). Another approach is the dehydration of glycerol (*292*, *293*). Dehydrogenation of a C-3 alcohol in the presence of a manganese catalyst also provides acrolein (*294*).

Acrolein has been made in flow on scale. With scaling down, it can be available in a laboratory, even though high temperature equipment is needed. The on-site preparation alleviates the need to transport a hazardous compound. However, its uses are limited and no major growth should be expected.

Singlet Oxygen

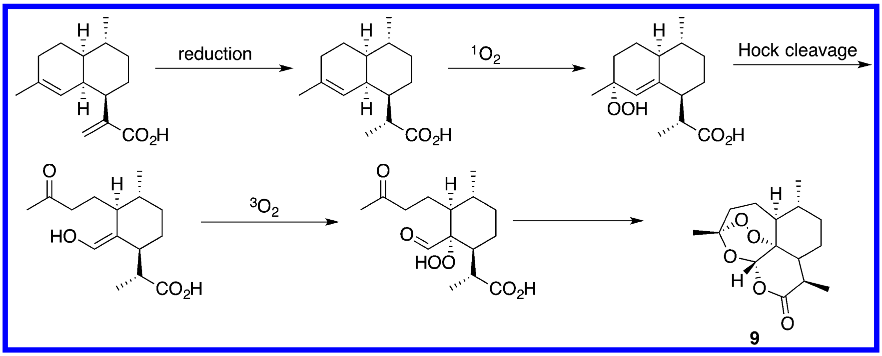
The use of a flow system allows for the *in situ* production of singlet oxygen in a photochemical reactor (*295*). The photochemical step makes the procedure amenable to flow. The substrate to be oxidized can be used as solvent (*296*). (For a discussion on photochemical reactors in flow see the following section.) A number of photosensitizers are available and supercritical CO_2 can be used to further reduce safety hazards (*297*).

Singlet oxygen can also be generated in the presence of a catalyst which is excited by a laser (*298*). A reactor system has been made where oxygen is not supplied directly to the reactor but through microcapillary films (*299*).

The photochemical oxidation of terpenoid substrates can be achieved by the generation of singlet oxygen in flow. This is accomplished by the addition of the substrate and oxygen to the photochemical reactor, which has an immobilized porphyrin (*300*).

Primary and secondary amines can be converted to the corresponding imines by singlet oxygen. Subsequent reaction with a nitrile provided the α-amino nitrile (*301*).

A flow system helped out in the synthesis of the antimalarial drug artemisinin (**9**) (Scheme 62). The sequence also uses triplet oxygen (*302–304*).



*Scheme 62. Synthesis of artemisinin (**9**) from artemisinic acid.*

Singlet oxygen can perform unique reactions. One of the main problems with its use in batch has been its photochemical generation; side reactions can be very problematic when other reactants are present. These are being overcome by the use of flow chemistry and the ability to use immobilized initiators. The use of this reagent will continue to grow.

Photochemical

The use of a flow system for photochemical reactions has a number of advantages. The narrow tubes allow good penetration of the light into the reaction medium. A reasonable flow rate removes the product before side reactions can occur. These factors can give rise to high quantum yields and much cleaner reactions.

For applications, such as the production of singlet oxygen, the photosensitizer can be immobilized into the reactor itself.

Photochemical reactions in flow have moved a long way from shining a light on a microreactor, which caused problems during scale-up due to longer cross sections. Better designed equipment is now available and this is seen as a growth area.

Ozonolysis

Ozone is a green oxidant as the usual by-product is water (*305*).

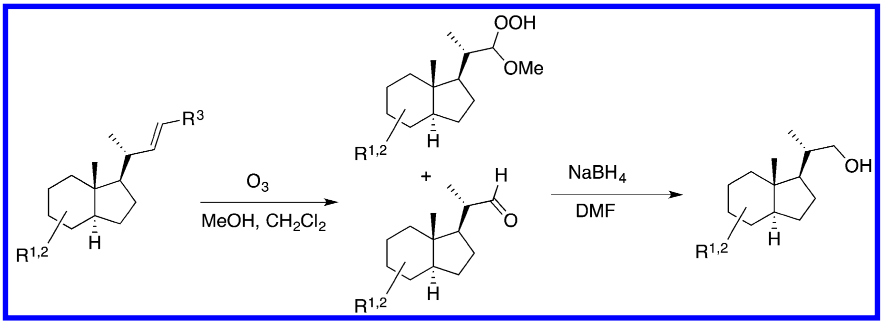
Unlike other oxidations, the intermediate ozonolides are highly explosive. This lends these reactions to use flow methods. The use of IR helps marry the rate of ozonolysis production with reaction rate and amount of the alkene present as it is introduced in a stream (*306*). Raman has also been used to monitor the reaction (*307*).

Ozone can be introduced through a semipermeable membrane. As illustrated in previous sections, this methodology can also be used to introduce other gases as well into a flow reaction (*308*). An alternative is to use a falling film reactor, which has been used in the oxidation of 1-vinylhexyl ester (*309*).

An alkene can be oxidized by ozone (*310–312*). The work-up can also be performed in flow (*313*). NO_2 and NO have also been used as co-oxidants to give the corresponding epoxides rather than cleavage products (*314*, *315*).

As part of a multistep sequence to 2-aminoadamantane-2-carboxylic acid (See Scheme 52; Grignards section), an ozonolysis was performed using a laminar flow regime in a PTFE tube (*122*).

In a two-step process ozonolysis in microstructured devices was used to prepare vitamin D analogs (Scheme 63) (*316*).



Scheme 63. Preparation of vitamin D analogs.

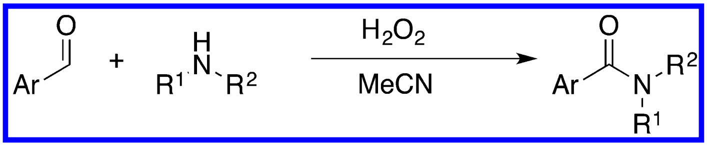
Ozone has been generated in flow for a long time, albeit in a gaseous flow. Now being able to couple this with downstream processing avoids the build up of the explosive ozonides. This is a useful methodology for the oxidation of alkenes, as the product can be determined by the reaction conditions.

Hydrogen Peroxide

Hydrogen peroxide is relatively unstable and can give rise to explosive mixtures (see also Hydrogen Peroxide Chapter). It quickly decomposes in the presence of many metal salts. This can give rise to a sudden pressure rise as oxygen gas builds up.

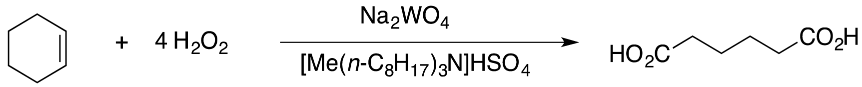
Hydrogen peroxide is a useful reagent that can be used to prepare peracids just prior to their reaction (*317*).

Benzaldehyde can be efficiently oxidized with hydrogen peroxide in flow with a membrane reactor (*318*). Amides can be prepared from a secondary amine, an aldehyde and hydrogen peroxide (Scheme 64) (*319*).



Scheme 64. Preparation of amides from benzaldehydes.

Oxidation of cyclohexene in the presence of a tungsten catalyst gave a more efficient route than the current process to the synthesis of adipic acid (Scheme 65). This permitted the reaction to be run at lower temperatures (*320–323*).



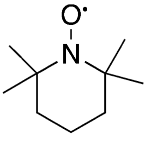
Scheme 65. Preparation of adipic acid from cyclohexene.

A herbicide was oxidized by Fenton's reagent and hydrogen peroxide generated *in situ* in an electrochemical flow reactor (*324*).

Hydrogen peroxide is a useful oxidant producing water as the by-product. Its instability with certain metals and the amount of gas produced during decomposition make handling of the compound somewhat hazardous in batch reactions. These can be alleviated by the use of flow. A modest growth is envisioned with flow reactions becoming more popular. It gains popularity versus other 'green' oxidants in that it does not requires an ozone generator or photochemical cell.

TEMPO Oxidations

TEMPO (**10**) has been used in batch mode for oxidations of alcohols to carbonyl compounds. Safety issues can be reduced when flow methodology is used for this powerful reagent. TEMPO can be immobilized for use in a continuous process (*325*). TEMPO is often used in substoichiometric amounts to reduce safety problems. This means that a co-oxidant has to be used. As an example, in the presence of a catalyst, dilute oxygen can be used as the co-oxidant (*277*).



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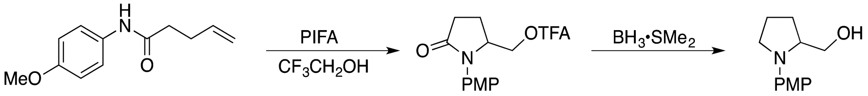
Bleach can also be used as the co-oxidant. This was used in a spinning tube-in-tube reactor (*326*).

NO is another cooxidant for these oxidations, which requires oxygen for recycle of the NO (*327*). Hypervalent iodine can also be the co-oxidant (*328*). Perhaps the greenest co-oxidant is the use of electrons as supplied in an electrolytic cell (*329*).

The use of TEMPO can have handling issues, although some can be minimized by the use of flow reactions. Modest growth should be seen as flow technologies become more established.

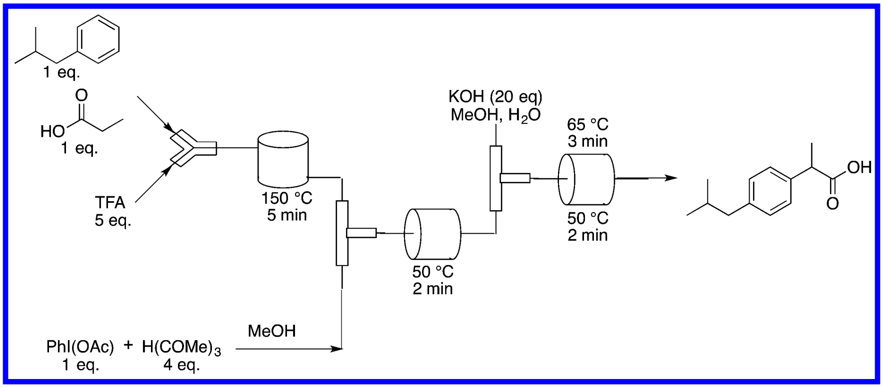
Hypervalent Iodine Compounds

Hypervalent iodine can be used as the oxidant in TEMPO mediated oxidations of alcohols (see TEMPO section) (*328*). It can also be used to bring about cyclizations (Scheme 66). The use of a stop-and-flow method minimized side reaction (*330*).



Scheme 66. Cyclization mediated by phenyliodine(III)-bis(trifluoroacetate) (PIFA).

In the adaptation of a synthetic scheme for the preparation of ibuprofen, hypervalent iodide was used as an oxidant to bring about a rearrangement (Scheme 67) (*331*).



Scheme 67. Synthesis of ibuprofen.

Hypervalent iodine compounds can be explosive. Work is continuing to find more stable forms.

Swern Oxidations

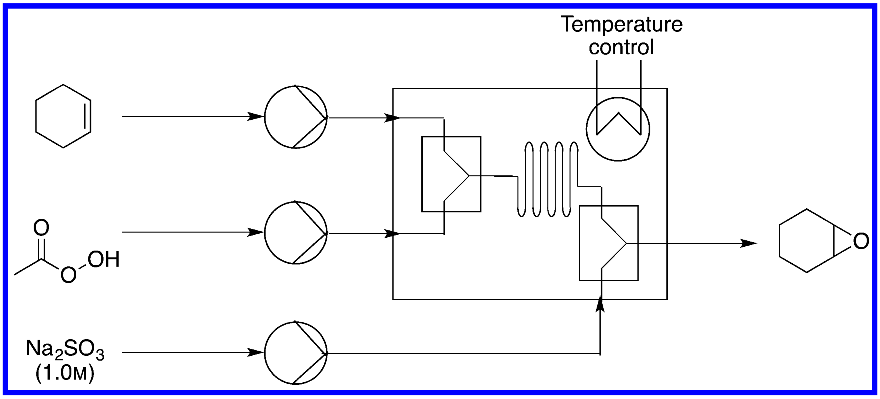
Swern oxidations avoid the use of heavy metals but the reagent still has safety issues. To avoid the use of cryogenic conditions, a semicontinuous process was developed. Dimethyl sulfoxide and alcohol were mixed with oxalyl chloride in methylene chloride in a flow system (residence times 0.1-1.4 s). The reaction was completed by being discharged into diluted trimethylamine (*332*). Alternative reactor systems have also been used to make it a completely continuous process (*333*, *334*). The exothermic Pummerer rearrangement is controlled by use of flow (*335*–*337*). This avoids the use of cryogenic conditions.

The use of a flow system also helps with the optimization of the reaction (*338*).

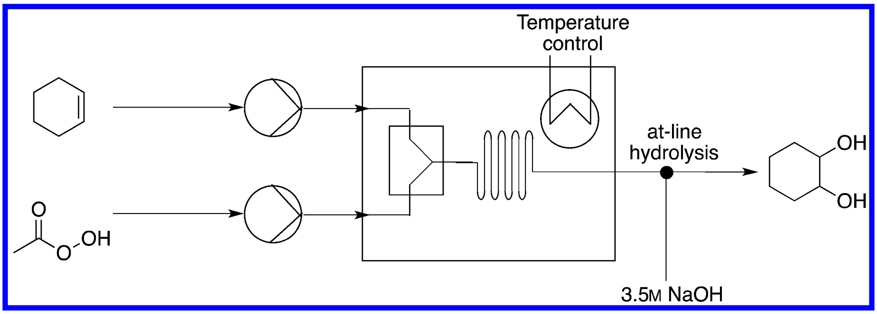
The Swern oxidation reagent system has stability problems and there has been a move away from its use. Some of these problems can be reduced by the use of flow. However, the development of alternative oxidation systems such as those described above will detract from major growth of this reagent system.

Other Oxidations

Peracids have been used in batch mode to bring about many transformations. Some of these have been converted to flow to minimize the stability problems associated with the peracids. The methodology has been used to prepare epoxides (Scheme 68) and dihydroxy compounds (Scheme 69) (*339*).



Scheme 68. Epoxide formation from an alkene.



Scheme 69. 1,2-Dihydroxy compounds from alkenes.

Hydrogen peroxide and peracetic acid will form the 1,2-diacetoxy product from an alkene in the presence of a palladium catalyst (*317*).

The use of peracids has been troubled by safety issues. These can be reduced by the use of flow technology as the peracid can be prepared immediately prior to use. The methodology would be much more powerful if asymmetric methods were available and, no doubt, this will be an area of research.

Summary

Flow methodology is now becoming a useful tool in the synthetic chemists tool box at laboratory scale and makes scale-up easier, particularly when issues regarding low temperature, intermediate's stability and potential for explosions need to be considered. This chapter has concentrated on mitigating the use of hazardous materials in accomplishing synthetic goals although many innocuous reactions, such as esterification, can be performed in a flow regime as well. As manufacturers continue to address the problems associated with running more reactions in flow, and additional chemists become more familiar with its advantages, the growth in this area should continue. Other than laboratory scale medicinal chemistry reactions, a chemical engineer should become involved in the reaction due to the engineering aspects of a good flow system. This collaboration will widen the chemist's knowledge and appreciation of the problems associated not just with the reactor but with downstream processing.

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Chapter 13

A New Paradigm in Oxidative Cleavage Reaction: The Use of Continuous Reactors To Enable Safe Scale Up of Ozonolysis

Ayman Allian[*]

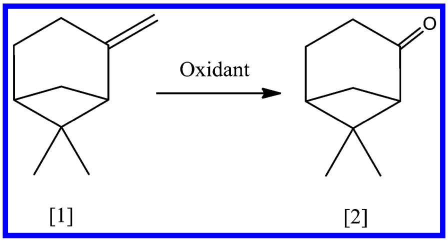
AbbVie, Process Research and Development, 1401 Sheridan Road,
North Chicago, Illinois 60064
[*]E-mail: Ayman.allian@abbvie.com

The formation of carbonyl compounds via oxidative cleavage of alkenes is an important synthetic step in API production. Ozone is an excellent oxidizing agent to perform this synthesis and is more efficient and environmentally friendly to current oxidation protocols that employ toxic metals. However, the exothermicity of ozonolysis reaction along with the instability of the intermediate involved hinders its implementation at scale in batch mode. In this chapter, we demonstrate that carrying out ozonolysis in continuous mode successfully addresses these safety thermal hazard concerns.

Introduction

Oxidative Cleavage Reactions

The oxidative cleavage of alkenes to form carbonyl compounds, primarily ketones and aldehydes, is an important tool for the organic chemist in the synthesis of pharmaceutical, complex natural products and fine chemicals including flavor, skin care and fragrance materials (*1–3*). A plethora of reagents such as potassium permanganate ($KMnO_4$) and sodium periodate ($NaIO_4$), catalyzed by $RuCl_3$ or OsO_4, have been used successfully to accomplish this type of transformation. An example of this important reaction is the synthesis of nopinone **2** from β-pinene **1** (Scheme 1). β-Pinene **1** is an abundant monoterpene natural product that is obtained by extraction of several plants and it is also a byproduct from the pulp and paper industry. The oxidation product, nopinone **2**, is an important building block used in the synthesis of pharmaceutical products (*4*) and chiral ligands (*5*).



*Scheme 1. Synthesis of nopinone **2** from β-pinene **1**.*

Several oxidants can promote the cleavage of β-pinene **1** (*3*). For example, high yields (95%) have been obtained using a combination of 4 equiv. $NaIO_4$ with a catalytic amount of $KMnO_4$ (20 mol%) (*6*). In other studies, a combination of $NaIO_4$ with either OsO_4 (*7*) or $RuCl_3$ (*8*) also furnished reasonable yields of nopinone [**2**]. The latter metal-catalyzed oxidations accomplished the desired reaction, however, the presence of trace metal in the final product is intolerable in the highly regulated cosmetic and pharmaceutical industries. Therefore, the use of metal based oxidants usually requires exhaustive post reaction purifications and expensive analytical examination to assure the absence of metals to ppm levels. Even after metal extraction from the product, these isolated highly toxic metals present a disposal challenge.

The need for a non-catalytic oxidant prompted our interest in another class of oxidant, namely ozone gas. Indeed, the use ozone as an oxidant, a process referred to as ozonolysis, has been successfully utilized to prepare nopinone from β-pinene (*9*). Historically at our research facilities, ozonolysis has been routinely practiced for small scale deliveries (<10 g). However, if the synthesis was to be scaled up, different oxidants, typically metal-based oxidants were utilized. We took the initiative to replace the metal species such as the toxic and volatile osmium tetraoxide with ozone as an alternative oxidant to produce quantities at kilogram scale starting with substrate that is structurally similar to β-pinene, a terminal alkene. We will detail our development of this work as well as a brief discussion of ozone formation and handling.

Ozone Formation

Ozone is formed by breaking the chemical bond of atmospheric oxygen (O_2) into two oxygen radicals which then combine with molecular oxygen to form ozone. The most common method of generating ozone is by passing a strong electric charge through oxygen, also referred to as corona discharge tube. In the corona discharge tube, electrons have sufficient energy to break the chemical bond of O_2 into radicals which leads to ozone formation. Strikingly, the use of corona discharge to form ozone mimics how ozone is formed in nature by lightning. The presence of ozone, in nature and in the lab settings, can be recognized because of its strong odor resembling chlorine.

Ozone gas is unstable, thus it is typically generated at the point of use and cant be stored. From an environmental point of view, a process that utilizes ozone gas is green because ozone is generated from O_2 and is decomposed back to O_2, and no toxic chemicals or metals are used. Any excess unreacted ozone can be safely decomposed using available commercial thermal and/or catalytic ozone destruction units.

Ozonolysis Advantages and Applications

Using the atom economy concept to evaluate the use of ozone as an alternative oxidant to metal-based oxidizing agents, clearly ozonolysis is the winner since the majority of reactant atoms end up in the product. Ozonolysis has two additional desirable features compared to other oxidants from a process chemistry perspective. First, ozonolysis can be carried out in a wide range of protic and aprotic solvents. Reaction solvents may include methanol, ethyl acetate, dichloromethane, ethanol and acetic acid. Second, ozonolysis is very selective for cleavage of alkenes in the presence of other oxidizable functional groups.

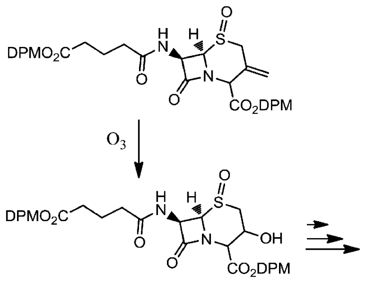
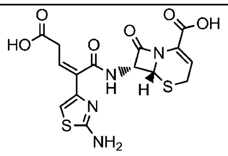
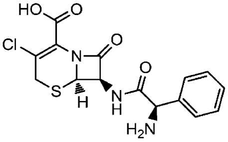
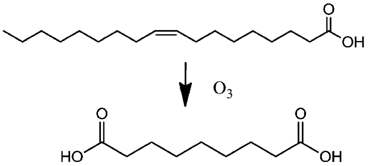
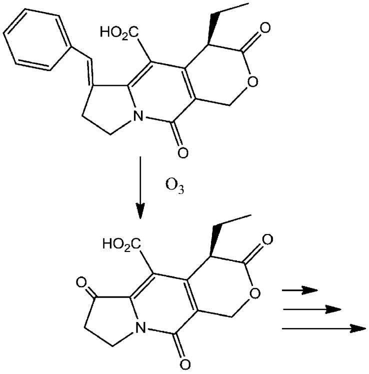
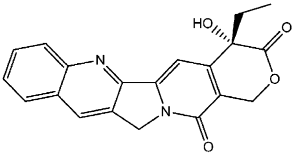
These advantages made ozone the oxidant of choice for a range of applications especially in the synthesis of the final product or the intermediates of key pharmaceutical and fine chemical products (see Table 1). Other examples include the synthesis of Vitamin D (*10*), Artemisinin (potent antimalarial) (*11*), and 1-monoesters of 2-ketoalkanedioic acids (*12*). Ozonolysis is also a key synthetic step in the formation of Indolizidine 251F (*13*), which is a potent alkaloid naturally found in poisonous frogs skin.

It is worth mentioning that the use of ozone is not limited to organic synthesis, it is also widely utilized as disinfectant in wastewater treatment plants and the supply of drinking water (*17*).

Ozonolysis Safety Concerns

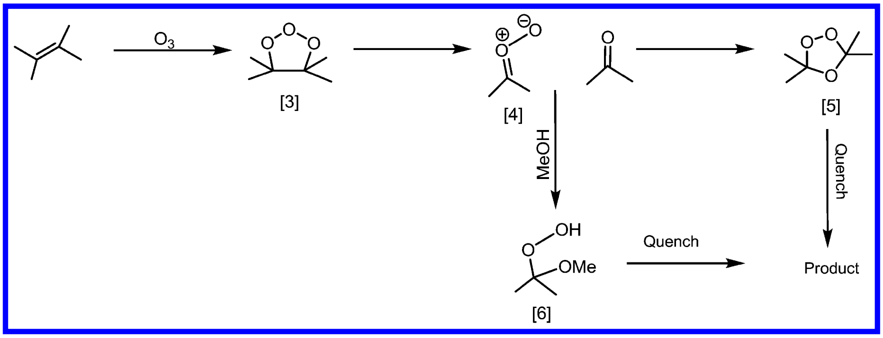
The practice of ozonolysis gives rise to several safety challenges that have the potential to restrict its wider use, especially on scale. First, ozone is toxic and levels as low as 5 ppm or higher are considered dangerous to life and health. The current Occupational Safety & Health Administration (OSHA) permissible exposure limit is 0.1 ppm based on an 8 h time weighted average. Second, the ozonolysis reaction involves the accumulation of highly energetic intermediates (to be discussed in the next section) which can potentially lead to explosions. Finally, during the course of ozonolysis, a stream of oxygen and ozone is fed to the reactor and thus combustion potential poses a serious risk, especially while working with flammable solvents. A common practice to mitigate this hazard is to dilute the oxygen concentration in the reactor headspace by adding a sufficient amount of inert gas to drive the concentration of oxygen below the minimum oxygen concentration (MOC) to prevent the formation of a flammable atmosphere (*18*).

Table 1. Key Pharmaceutical and Fine Chemical Products for which Ozonolysis was Utilized in Its Synthesis.

Reaction	Product	*Use and (Reference)*
	 Ceftibuten  Cefaclor	Antibiotic[14]
	Azelaic acid	Treat Mild to Moderate Acne[15]
	 D,L-Camptothecin	Antitumor Activity in Various Cell Lines[16]

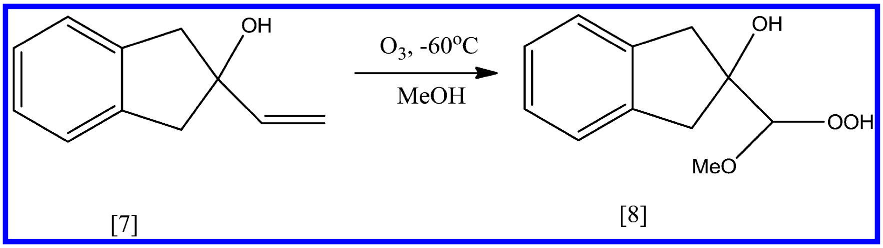
Energetic Intermediates and Thermal Analysis

Based on the well-accepted mechanism for the ozonolysis of alkenes (Scheme 2) by Criegee (*19*), the reaction proceeds by the addition of ozone to the alkene to form the highly energetic primary ozonide **3**. The latter is very unstable but has been isolated at temperatures as low as -238 °C. At temperatures relevant to this study, >-50 °C, the primary ozonide cleaves to form an aldehyde and carbonyloxide **4** which recombine to form the more stable secondary ozonide **5**. The formation of hydroperoxides **6**, especially in protic solvents, such as methanol, cannot be ruled out. Indeed, aqueous or polar systems are the preferred solvents for ozonolysis as they promote the decomposition of the formed ozonide to the less energetic hydroperoxides species. Finally, the secondary ozonide can be further manipulated to form the desired products, either through oxidation to form carboxylic acids or by reduction to afford ketones, aldehydes or alcohols.



Scheme 2. General Reaction Mechanism of Alkene Ozonolysis

The ozonides **3** and hydroperoxide **6** are of particular interest because they are extremely unstable and can create potential explosion hazards especially when present at high concentrations. Indeed, a safety evaluation (*20*) of the β-pinene ozonide reaction mixture (Scheme 1) showed a severe and fast self-decomposition with an onset temperature 48 °C. In another safety evaluation of the ozonolysis of a terminal alkene substrate similar to β-pinene **1**, the DSC of an ozonized reaction mixture of tertiary allylic alcohol **7** to form hydroperoxide **8** by Ragan and co-workers (Scheme 3) showed an exothermic event at 45 °C (*18*). In order to ensure safety well below this relatively low temperature dictates that ozonolysis be conducted at a cryogenic temperature of ~ -60 °C in order to enforce a 100 °C safety margin (a common safety practice in the industry) between operating temperature and the onset temperature of a severe exothermic event.



Scheme 3. Ozonolysis of Allylic Alcohol 7

Ozonolysis Reaction and Quench Exothermicity

During any ozonolysis, keeping the process temperature below the onset temperature of the decomposition of ozonide or hydroperoxide is critical. Besides heat losses to surroundings, maintaining these cryogenic temperatures is a challenging task due to the inherent exothermicity of ozonolysis. Consequently, quantitative understanding of the exothermicity becomes a matter of paramount importance and it is typically experimentally obtained using calorimetric techniques such as Reaction Calorimetry (RC) or Accelerating Rate Calorimetry (ARC). However, there has been increased interest in using predictive techniques to estimate heats of reaction to corroborate experimental data and for obtaining an initial assessment of a synthetic route when experimental measurement is not feasible or practical (*21*). Indeed, Pfizers global process safety laboratories have adopted the use of heat of reaction estimation techniques especially in chemistries where predictive heat of reaction is in good agreement with the experimentally measured values (*22*).

The most common techniques used to estimate the heat of reaction is simply to calculate the difference between heats of formation of the reactants and products, where heat of formation is estimated using Benson group increment theory (*23*). While the latter approach is fast and can be precise for smaller molecules, it suffers from potential inaccuracy largely due to the fact that the approach does not take into account ring strain as well as intermolecular and intramolecular interactions. At our research facilities, the use of density functional theory (DFT) computational chemical methods was utilized as a predictive tool for the heat of reaction. Obtaining the heat of reaction using theoretical chemistry aids in understanding the inherent heat of reaction. Experimental techniques, such as (RC), can be biased as it measure the sum of all heat generated during the reaction which encompass, beside enthalpy of reaction, heat generated by other phenomenon taking place during reaction such as crystallization and vaporization.

The heat of ozonolysis reaction was evaluated using a CBS-QB3 (*24*) method implemented within Gaussian 03. Isobutylene was used as a model compound for terminal alkenes i.e. similar to β-pinene **1** and tertiary allylic alcohol **7** substrates discussed earlier. Furthermore, isobutylene resembles the substrate of interest in our laboratory that will be discussed later. DFT was utilized to calculate the heat of reaction of the relevant kinetic steps (Scheme 2) namely the formation of the secondary ozonide and its subsequent quench to the desired product with dimethylsulfide as shown in Figure 1.

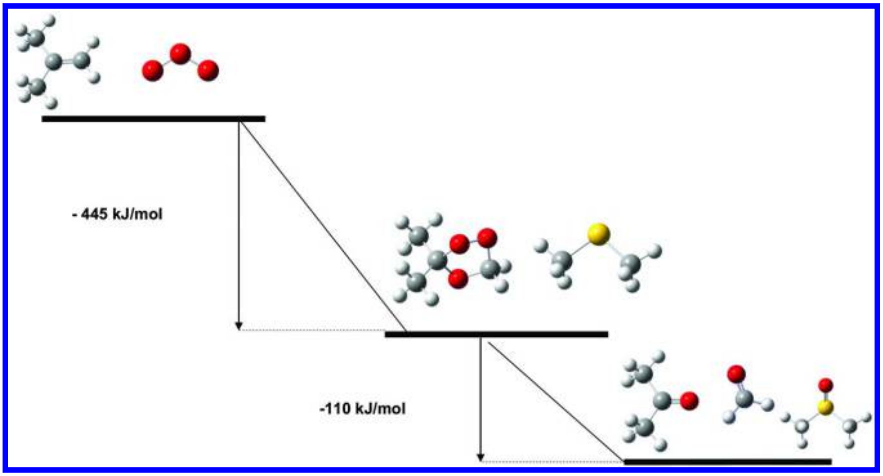


Figure 1. Calculation of Enthalpy of Reaction for Isobutylene Ozonolysis

The results from the current DFT analysis indicate that ozone addition to form the secondary ozonide is very exothermic with heat of reaction of -445 kJ/mol. The results are in excellent agreement with calculated energy for the reaction of ethylene with ozone where the heat of reaction to form the secondary ozonide was -427 kJ/mol (*25*). The latter results from computational chemistry are also in good agreement with the experimental calorimetric results from Pfizer (Scheme 3) where the measured heat of reaction of ozone addition was 535 kJ/mol (*18*). These predictions are also in good agreement with the calorimetric measurement of β-pinene ozonolysis (Scheme 1) where the heat of ozone addition is 499 kJ/mol (*20*).

Both experimental and computational methods show that ozone addition is very exothermic. In order to obtain a tangible sense of the consequences of the generated heat in the lab or at plant scale, the adiabatic temperature rise (ΔT_{ad}) associated with the exothermic event is calculated based on Equation 1. ΔT_{ad} reflects the theoretical temperature increase if generated heat is perfectly retained within the vessel. This is a useful value to determine since it gives a measure of the temperature rise of a reaction due to absence and/or loss of cooling.

$$\Delta T_{ad} = \frac{\Delta H_{net}}{m_{total} C_{p,r}} \tag{1}$$

where for every gram substrate, ΔH_{net} is heat evolved (in J), m_{total} is total mass of reactor contents in (g), and $C_{p,r}$ is the average heat capacity of the reactor contents (in J $g^{-1}K^{-1}$) (*38*). Utilizing the predicted heat of reaction calculated via DFT, the corresponding adiabatic temperature rise of the ozone addition to isobutylene reaction can be calculated using Equation 1 and was found to be 216 °C. In other words, if the energy of the reaction was released and the heat was not removed, the reaction mass could self-heat by 216 °C which reflect the intrinsic danger of running ozonolysis, even at cold temperatures. For example, if the reaction was carried out at the intended -60 °C, in the event of loss of cooling, the temperature can rise to 140 °C which is well beyond the onset temperature of ozonide/hydroperoxide decomposition. These temperatures are higher than the boiling points of the typical solvents used for ozonolysis and thus raises the potential for a catastrophic explosion. This exercise demonstrates the usefulness of using predictive methods, where a rapid understanding of the thermal severity of a reaction can be obtained before conducting the calorimetric experiments.

It is worth mentioning that ozone addition is typically a dose-controlled reaction. Therefore, a slow addition of ozone, along with the deployment of appropriate engineering controls, can keep the temperature below the onset of decomposition of the oxygenated intermediate and thus mitigate the risk of a runaway reaction. For example, during the ozonolysis of tertiary allylic alcohol **7**, charging ozone over 18 h, the team at Pfizer was able to maintain a temperature of -60 °C. Furthermore, the fact the reaction is dose-controlled also means that if the reactor temperature approached the decomposition onset temperature of the oxygenated intermediates, stopping the flow of ozone would immediately stall the reaction. This will be experimentally demonstrated in this study as a further layer of safety for our process.

DFT results also show (Figure 1) that the subsequent quench with DMS was also exothermic: 110 kJ/mol. DMS was used in our laboratory because of the ease of workup to remove its byproduct, DMSO, by simple water extraction. The heat generated by the quench corresponds to a 52 °C adiabatic temperature rise, which can again risk reaching the onset temperature of ozonide decomposition as the quench is conducted at 0 °C. It is worth mentioning that ozonide reduction rate via DMS is slow. Other more potent reducing agents have been used such as triphenylphosphine, trimethylphospine and thiourea (*26*). The latter reagents and their oxidized byproduct can be difficult to remove with aqueous washes. Recently, polymer-supported triphenylphosphine and thiourea were used where purification can be accomplished simply by filtration (*27*).

Performing an Ozonolysis Reaction

Traditional Batch Process

Ozonolysis has traditionally been carried out in batch mode despite the challenges discussed in the previous section, namely its inherent exothermicity along with energetic intermediate formation. However, implementing the proper engineering controls can significantly reduce safety concerns. In a typical batch mode operation, the olefin starting material solution is added to the reactor and then cooled to cryogenic temperature (<-50 °C). Then, air or pure oxygen is supplied to the ozone generator. The outlet of ozone generator is immersed in the substrate solution and ozone is charged until the substrate is completely consumed to ozonide/hydroperoxide. When the substrate is consumed, the reaction mixture turns blue as ozone saturates the solvent. Other process analytical tools (PAT) can also be utilized to ensure substrate depletion, namely in-situ IR. During the course of ozonolysis, the kinetics of ozone is so fast that little to no ozone is detected in the reactor headspace. However, moments after substrate is consumed, excess unreacted ozone is detected in the headspace and thus an ozone detector can be used as PAT tool as well.

After substrate consumption, the ozone generator is turned off, dissolved ozone is sparged from the solution and the reaction mixture is quenched with appropriate reagent to form the desired product. At this stage of the process, the reader can recognize the major drawback of batch mode ozonolysis because it involves the complete transformation of the olefin to its respective ozonide and hydroperoxide. This accumulation of energetic intermediates in batch mode can be resolved by carrying out the reaction in continuous mode where only a portion of the substrate solution is exposed to ozone and converted to ozonide at any time during reaction, significantly reducing the inventory of hazardous intermediates.

Continuous Processing

Continuous processing has gained increased attention for carrying out highly exothermic reactions and for reactions where energetic intermediates are formed (*28*). This is due in part to the fact that continuous processing utilizes smaller reactor volumes and thus offers higher heat transfer rates while minimizing the inventory of energetic intermediates. Ozonolysis, being inherently exothermic and associated with the formation of unstable intermediates, is an ideal candidate for flow chemistry.

One of the earliest examples of carrying out ozonolysis in a flow mode was reported by the Jensen group (*29*). The reaction was conducted in multichannel microreactors fabricated from silicon and Pyrex wafers. Realizing that the reaction is mass transfer limited, the team microfabricated silicon posts inside these channels to further enhance mass transfer (Figure 2). The setup was successfully used for the ozonolysis of phosphite, amine, and 1-decene, delivering high conversion in short contact times as low as 1 s. Besides the multichannel microreactors, other microstructured reactors have been successfully used for ozonolysis including falling film microreactors and a cyclone mixer (*10*).

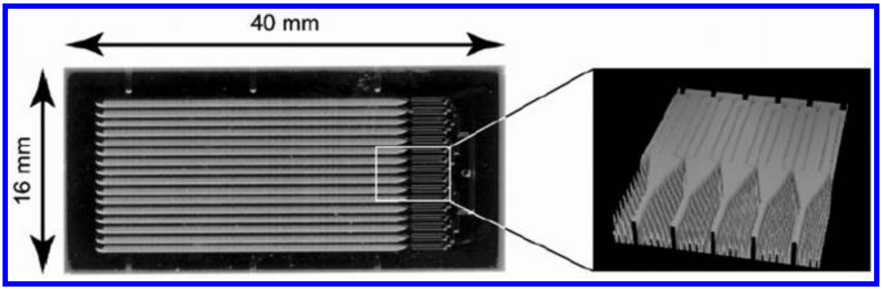


Figure 2. Picture of microfabricated multichannel microreactor along with details of the microfabricated silicon posts used to enhance mass transfer. (Reproduced with permission from reference (29). Copyright (2006) American Chemical Society.)

Interestingly, the Jensen group conducted ozonolysis reactions at 0 °C without the need of cryogenic temperatures (*29*). From safety perspective, continuous processing at temperatures close to the onset temperatures of a thermal event can be better tolerated in a flow mode, as compared to a batch process. In terms of safety, heat removal is superior due to the high surface-to-volume ratio. Thus, the reaction temperature can be prevented from approaching the decomposition temperature. In a batch process, hotspots and poor heat transfer from the jacket to the reactor contents require operations at temperatures well below the onset temperatures to ensure safety. Furthermore, flow mode provides the benefit of the use of smaller volume reactors even at scale. Therefore, even if the onset temperature was reached during the reaction, the inventory of highly energetic material present in the flow apparatus is small thus the consequences of a runway reaction are reduced. Within the context of continuous ozonolysis, only a fraction of the total substrate is converted to the energetically oxygenated intermediates at any one time. Under the worst case scenario of reaching the onset temperature, the severity of the decomposition is mitigated due to small volumes of flow reactors i.e. low quantities of materials. On the other hand, reaching the onset temperature in a batch mode ozonolysis, especially at the point where all substrate has been completely converted to ozonides/hydroperoxide before quenching, can have catastrophic effects.

Furthermore, batch processes with unstable reagents/products are conducted at cryogenic temperatures to retard the kinetics of their decomposition reactions at the higher temperature. On the other hand, flow chemistry allows synthetic chemists to access higher temperatures because although the kinetic of decomposition is faster, the contact time is tightly controlled. These energetic reagents will only be exposed to reaction conditions for only a very short time before being quenched via reacting with another reagent or simply entering a quench tank.

Another interesting ozonolysis example makes use of a tube-in-a-tube setup. Ozone from the outer tube is transferred through a semipermeable Teflon AF-2400 inner tube to where an alkene stream is flowing (*27*). The setup developed by Ley and his coworkers was successfully utilized to carry out ozonolysis in flow mode on a series of alkenes at a rate of about ~0.1 g/hr of products. However, the latter tube-in-tube setup was not efficient in absorbing ozone and thus a 1 h residence time in the apparatus was required to achieve high yields. As the latter system is not suited for direct scale-up, the team later developed a simple, high-performance setup to enable processing of larger quantities of substrate (*30*). This new setup consists of PTFE connector followed by a PTFE tube for additional residence time. Inside the T-connector, the liquid stream is directly sprayed into an ozone stream (Figure 3-A). This spraying effect leads to excellent mass transfer which resulted in quantitative reaction in a short residence time (15 s). The enhancement of ozone mass transfer increases the throughput to potentially 6.6 g/hr and also required a small excess of ozone (1.5−2 equiv). It is worth mentioning that the higher gas-to-liquid ratio inside the tube resulted in a flow pattern where the liquid wets the surface while the gas tunnels through the middle of the PTFE tube (Figure 3-B) (*31*).

Recently scientists have begun to have access to off-the-shelf flow ozonolysis setups such as the O-Cube™. Fabricating a flow ozonolysis setup can be cumbersome as it requires significant resources in terms of constructing the appropriate reactors and finding the right pumps and of course having the appropriate temperature controls in place. The O-Cube removes these hurdles as all the latter components are built-in, even an ozone generator is available. However, the setup is designed for small scale deliveries and not suitable for scale up. Irfan and coworkers (*32*) successfully carried out ozonolysis on a wide range of olefins using the O-Cube™ including β-pinene (Scheme 1). While the batch mode ozonolysis of β-pinene required cryogenic temperature (*9*), the use of the O-Cube™ allowed the ozonolysis to proceed at room temperature with high yields (70%).

Lonza recently developed a ton-scale continuous ozonolysis apparatus (Figure 4) which was successfully used for the conversion of chrysanthemic acid to its corresponding aldehyde (Scheme 4) (*33*).

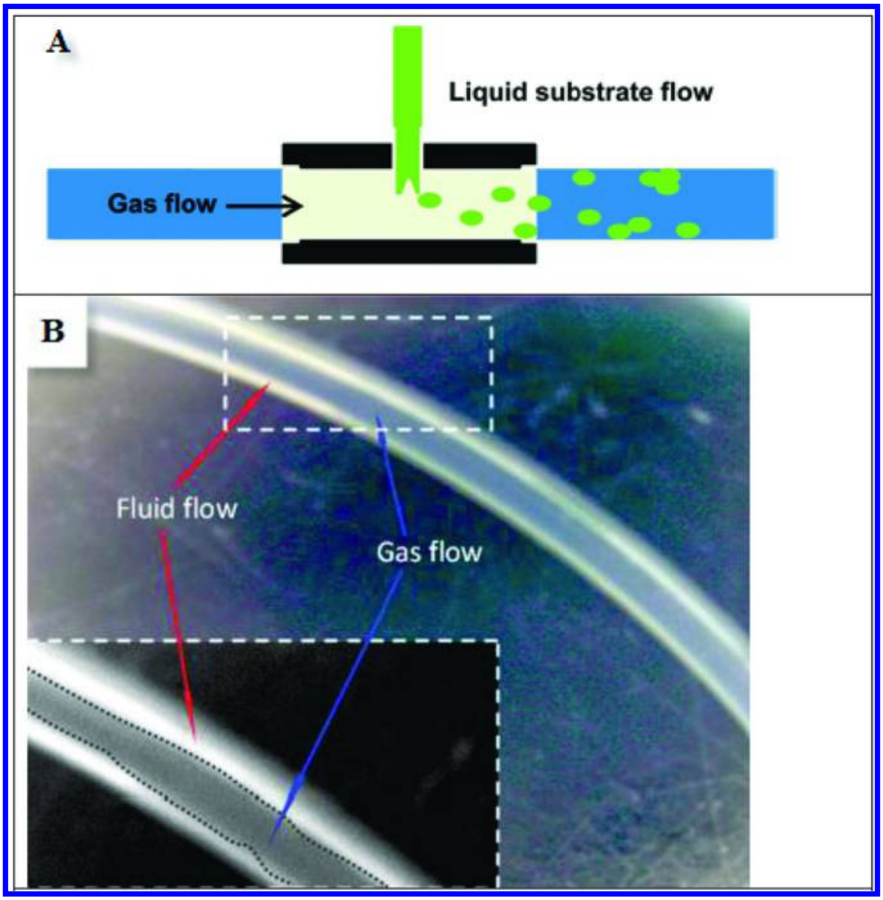
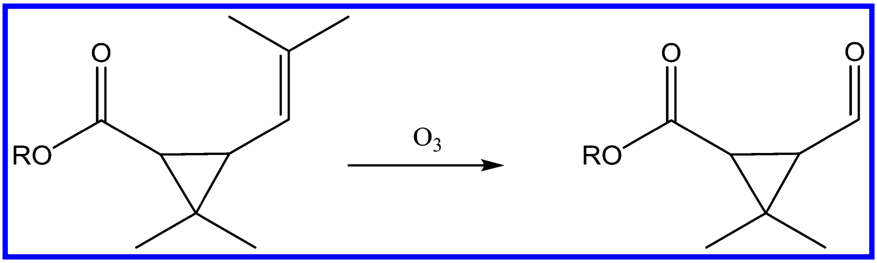


Figure 3. Schematic of PTFE T-connector. Wavy-annular flow pattern observed inside the reactor coil in the ozonolysis reaction. (Reproduced with permission from reference (30) (2012) American Chemical Society.)



Scheme 4. Ozonolysis of the chrysanthemic acid to its corresponding aldehyde

After mixing the ozone supply into the substrate stream, the setup employed commercially available static mixing elements within the tube to increase ozone mass transfer and achieve high yields. Please note that a ratio of the stream leaving the reaction zone (mixture of product and starting material) is recycled back to the ozone rich area to improve the conversion, nevertheless over-oxidation of the product was not observed.

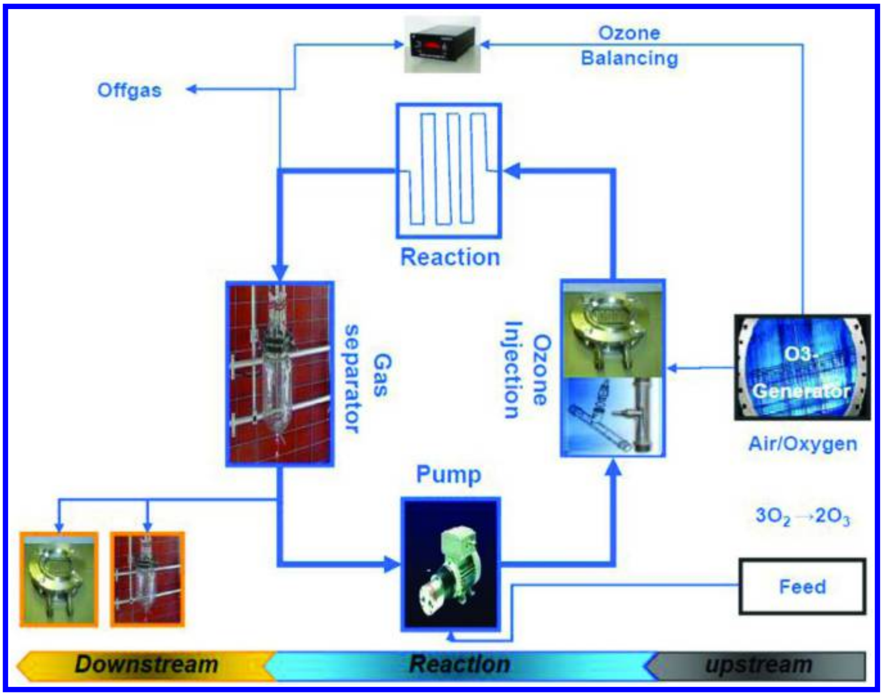


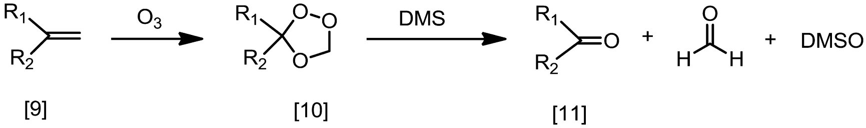
Figure 4. Schematic representation of Lonza ozonolysis production train. (Reproduced with permission from reference (33) (2011).)

The flow setups discussed to this point can be described as plug flow reactors (PFRs). The author explored the utility of another flow approach namely continuous stirred tank reactor (CSTR) (*34*). CSTR proved to be a powerful approach to carry out ozonolysis as will be shown in the next section. To our knowledge, this represents the first successful continuous ozonolysis in a CSTR rather than PFR.

It is well known that the ideal PFR has the property that all components of the incoming reactant stream experience a very similar residence time inside the reactor. However, CSTR residence distribution has a wide range. In other words, if a CSTR reactor was used for ozonoloysis, portions of the substrate stream entering the CSTR can be exposed to ozone for a significantly longer period of time while other segments of the stream would spend a shorter time in contact with ozone. Strikingly, this wide distribution of ozone contact time in CSTR was inconsequential to yield and selectivity. The ozonolysis kinetics are very fast and therefore, the segments of the incoming substrate stream that have short exposure to ozone still have sufficient contact time to react. On the other hand, the segment of the substrate solution that has a long contact time with ozone did not show evidence of over-oxidation of the product, as observed both in our laboratories and at Lonza (*33*). These conclusions can be substrate specific and thus careful kinetic evaluation of the reaction is needed for other examples.

Development of an Ozonolysis Process

At our facility, there was a need to carry out an oxidative cleavage of a terminal alkene intermediate **9**, structurally similar to β-pinene **1** and allylic alcohol **7**, to form the corresponding carbonyl compound **11**. The structure of the intermediate and the aldehyde is proprietary, however its generic structure is shown in Scheme 5.



*Scheme 5. Ozonolysis of the Substrate of Interest **9***

For the oxidative cleavage, ozonolysis was proposed as an alternative to the existing osmium tetroxide based oxidation process. With the awareness of the risk of carrying out ozonolysis based on the predictive heat of reaction calculated with DFT using isobutylene as a model compound, the next step was to carry out experimental thermal analysis of the ozonolysis reaction. Furthermore, the effort to replace the batch mode process with a flow process required a thorough understanding of reaction rate. Therefore, a kinetic screening of the ozonolysis reaction was conducted to ensure successful scale up of the process.

Thermal Stability

At our process safety laboratory, isolated olefin reactant **9** and product **11** were examined by DSC and no significant thermal hazards were observed. Afterward, ozone addition exothermicity to form the corresponding ozonide **10** was investigated using a Mettler-Toledo RC1 reaction calorimeter. The RC1 allows accurate determination of heat flow and the enthalpy change associated with a chemical reaction at conditions very close to those of industrial scale.

During the ozone addition reaction in the RC1 (Figure 5), the observed total heat evolution was -381 kJ/mol with adiabatic temperature rise of 187 °C in excellent agreement with previous studies that measured adiabatic temperature (186 °C and 170 °C) (*18*, *20*) for the similar molecules β-pinene **1** and allylic **7** alcohol ozonolysis addition, respectively. Furthermore, the results are also in agreement with the heat predicted by computational modeling carried out by the author (-445 kJ/mol). The lower experimental value for the heat of reaction compared to the one calculated by DFT can be explained that experimentally, a small fraction of the solvent from the RC1 was lost by entrainment due to gas (ozone/oxygen) active bubbling during ozone addition reaction. As the latter process is endothermic, it can potentially underestimate the inherent heat of reaction.

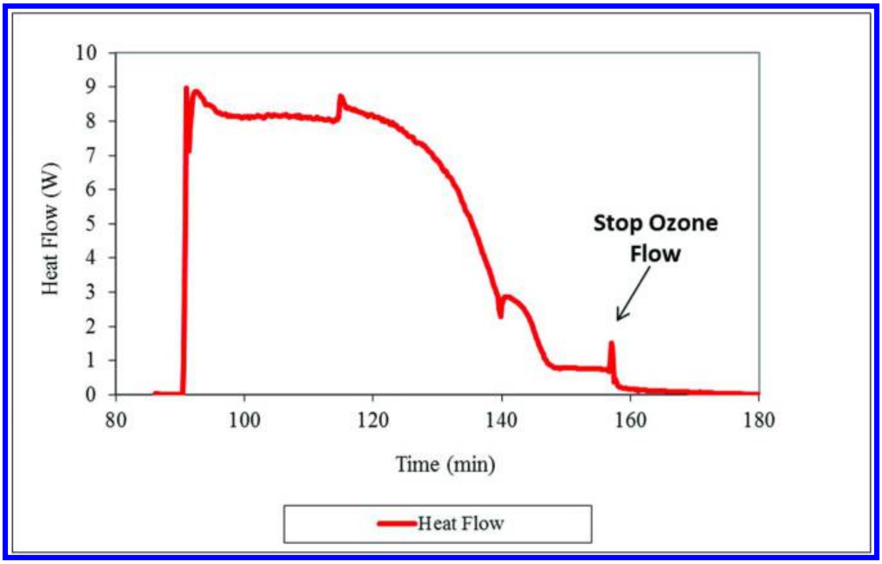


Figure 5. RC1 Heat Flow Results for Ozone Addition to Olefin ***9***

At the end of ozonolysis, the reaction mixture was held at -45 °C and purged with nitrogen to remove excess ozone. Then a sample of the ozonized reaction mixture was examined by DSC. An exothermic event occurred at 42 °C in good agreement with β-pinene (*20*) and allylic alcohol (*18*) ozonides which have onset temperatures of 49 °C and 45 °C, respectively.

Next, the reaction mixture in the RC1 was warmed to 0 °C to allow the investigation of heat generated during the quench with DMS. The observed total heat evolution was -122 kJ/mol in excellent agreement with the value of -110 kJ/mol calculated by DFT.

The quench with DMS was not addition controlled as was observed for the ozone addition. Indeed, the reaction was very slow and persisted for at least two hours after the addition of DMS, as evident by the heat flow (Figure 6). Thus, extreme caution is needed to confirm that the ozonide/hydroperoxide have been completely quenched. At our laboratories, the quenched solution was held until less than 1 ppm peroxide is present

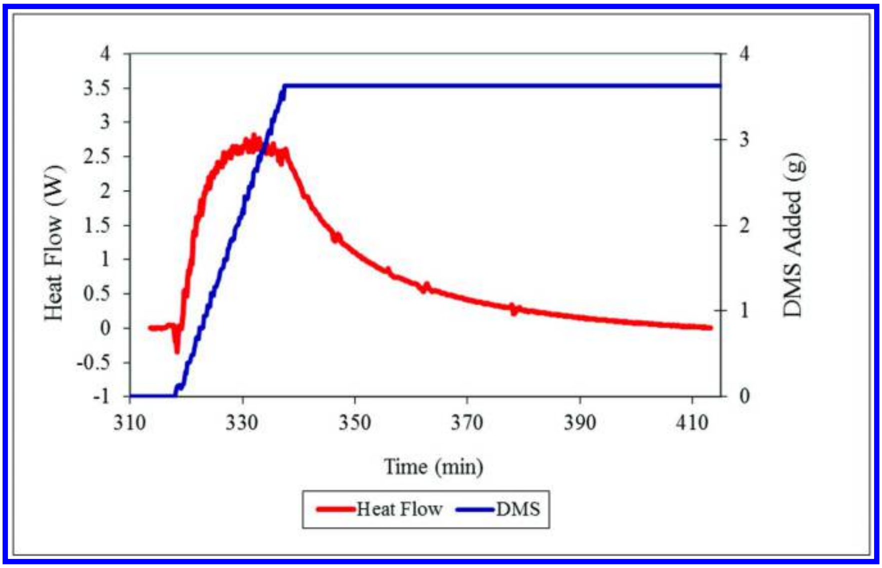


Figure 6. RC1 Heat Flow Results for the olefin ***9****; methyl sulfide quench*

Kinetics of Batch Ozonolysis Using Styrene as a Model Compound

Once testing established we could proceed safely in the laboratory, the rate of the ozonolysis reaction in the traditional batch process was explored. In these experiments, styrene was utilized because it is also a terminal alkyne and thus a representative model compound to the substrate of interest. For these experiments, a lab scale reactor that was equipped with an FTIR fiber optic probe to monitor reaction progress was assembled and connected to an ozone generator (Figure 7).

The addition of styrene to methanol at -50 °C resulted in an infrared band at 780 cm^{-1}. When another equal amount of styrene was added, the band approximately doubled (Figure 8), indicating that FTIR is a viable analytical tool to quantitatively monitor styrene concentration. Ozone was introduced to the reactor for ~25 min and the concentration of styrene dropped linearly as evident from FTIR absorbance. The rate of styrene reaction with ozone (2.2 mmol/min) based on the FTIR signal, is almost equivalent to the ozone supply 2.3 mmol/min in agreement with the calorimetric test that showed reaction to be dose-controlled. This indicates that the reaction is limited only by ozone supply and the current setup is allowing sufficient gas-liquid contact for mass transfer to absorb ozone from the supplied gas stream.

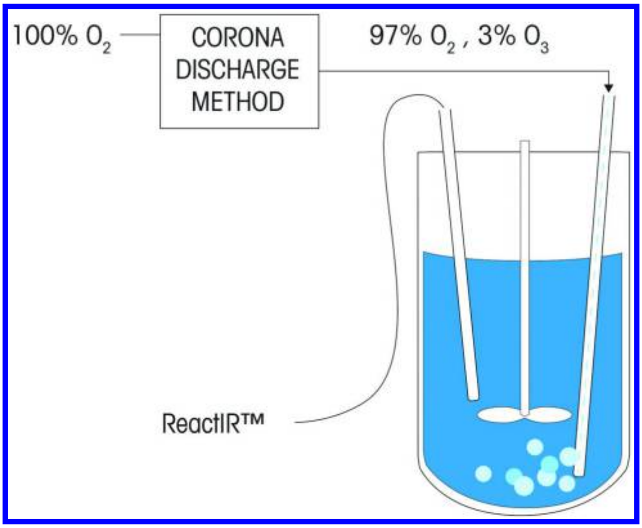


Figure 7. Experimental Setup of Batch Mode Ozonolysis of Styrene Equipped with ReactIR™ In Situ Analytics. (Image courtesy of Mettler Toledo (35))

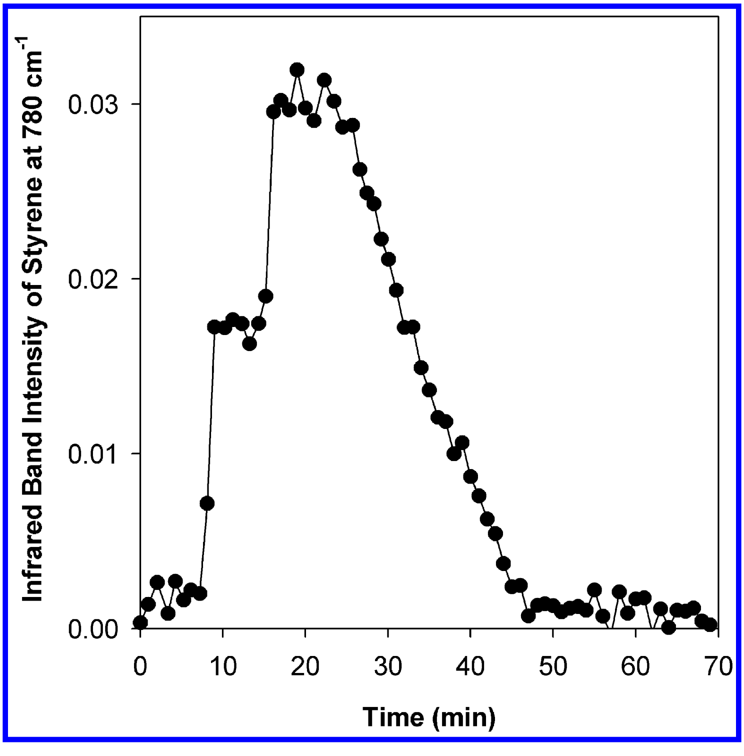


Figure 8. Infrared Band Intensity of Styrene at 780 cm^{-1} During Ozonolysis in Batch Mode. (Reproduced with permission from reference (34) (2011) American Chemical Society.)

The batch experiment indicates that the ozone reaction with styrene is fast and thus no ozone accumulation is expected in the reaction mixture. This was experimentally evaluated using the same setup described earlier with the exception that the ozone supply was purposely stopped before complete styrene consumption. Initially, ozone was introduced and in agreement with the previous semi-batch experiment, styrene concentration dropped linearly at a rate of about 2.2 mmol/min. After 35 min (i.e. 15 min after introducing ozone) ozone supply was halted and concurrently the reaction ceased, as evident by styrene concentration reaching a steady value (Figure 9 at ~40 min). After another 10 min, the ozone generator was turned back on and the reaction immediately started again at approximately the same rate observed prior to ozone interruption. These results indicate a fast reaction between ozone and the styrene in the liquid phase and both ozone absorption rate and olefin conversion do not depend on ozone mass transfer with current reactor geometry.

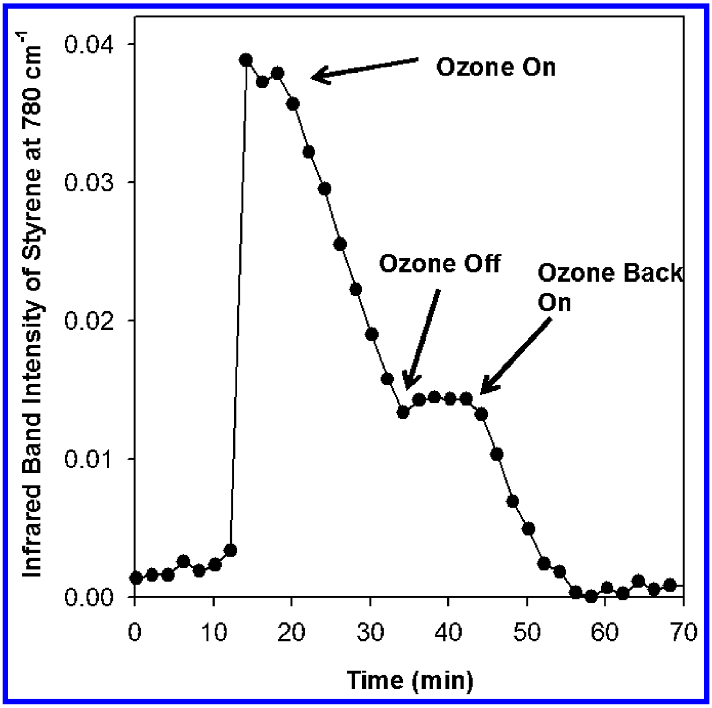


Figure 9. Infrared Band Intensity of Styrene at 780 cm^{-1} During Ozonolysis in Batch Mode With Ozone Supply Interruption. (Reproduced with permission from reference (34) (2011) American Chemical Society.)

Styrene Ozonolysis in a Continuous Stirred Tank Reactor (CSTR)

Simple Continuous Stirred Tank Reactor Fabrication

Encouraged by the high efficiency of ozone absorption within a standard batch lab reactor in the previous section, one of these existing reactors was retrofitted to allow continuous operation by adding an overflow valve. An overflow design was selected because of its simplicity in terms of fabrication for an existing reactor (Figure 10). In addition, this simple approach also avoids the need for a second pump to transport the CSTR contents to a third tank, usually a quench vessel, and simplifies the level control in the reactor to maintain a constant volume in the reactor.

Figure 10. A standard 100 mL lab reactor retrofitted by adding an overflow valve to allow continuous operation.

Residence Time in CSTR Versus Plug Flow Reactors

As mentioned before, the majority of continuous ozonolysis apparatuses utilize micro-reactor and tubular reactors where the flow regime resembles a plug flow reactor (PFR). The reactor used for our work is a CSTR. The mixing performance inside a PFR/CSTR can be characterized by residence time distribution (RTD) (*36*) analysis. It provides information on how long the various fluid elements have been in the reactor.

In an ideal plug flow reactor, if the fluid entering the reactor was divided into elements, then every element spends a similar time inside the reactor (*37*). On the other hand, fluid residence time in CSTR is more involved due to back mixing. If the incoming fluid stream, entering an ideal CSTR, is divided up into elements, each element entering the CSTR spends a different time inside the reactor. Significant divergence from ideal CSTR RTD is typically due to channeling and a dead zone. As regards the retrofitted reactors (Figure 10), channeling can result from feed fluid elements entering the reactor and quickly bypass it to exit at the overflow valve, spending little time inside the reactor. On the other hand, dead zones in the CSTR reactors can arise from having regions that are not thoroughly mixed and thus if elements of the fluid enter these region, they will only slowly be removed from the reactor to the overflow valve.

Prior to using the retrofitted CSTR reactors (Figure 10), a residence time distribution (RTD) analysis was carried out to ensure we possessed good mixing. The RTD test of the 100 mL retrofitted reactor was initiated by filling the reactor with 100 mL heptane, and adding 2 mL of acetone. The acetone strong FTIR intensity at 1218 cm^{-1} doubled (Figure 11) when an additional 2 mL of acetone was added, indicating a linear response to acetone concentration.

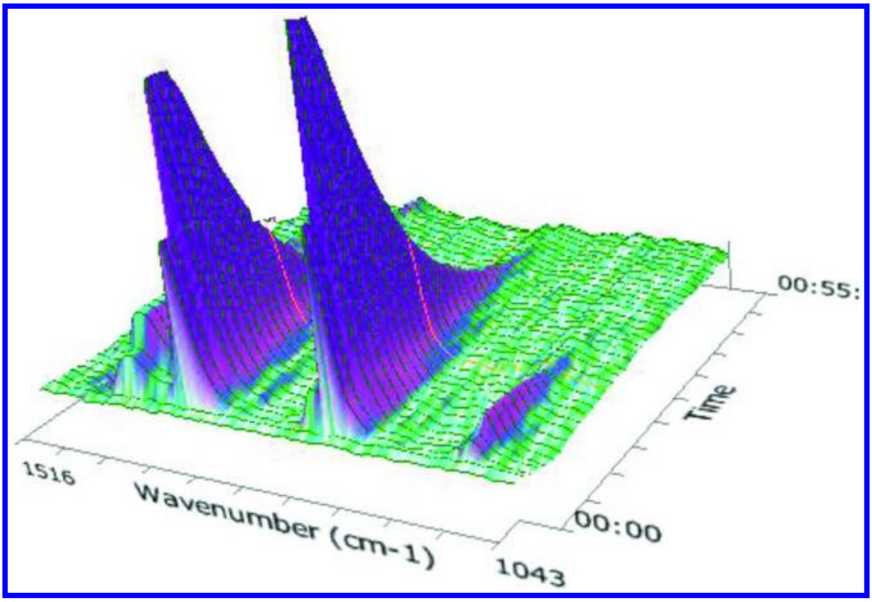


Figure 11. Infrared spectra of Acetone in Heptane during Residence Time Distribution Evaluation.

By introducing pure heptane to the 100 mL CSTR and allowing liquid to overflow to a receiving tank, the acetone concentration should decay according to Equation 2, assuming RTD in the current retrofitted reactors resembles that of an ideal CSTR

$$C(t)/C_o = e^{-t/\tau} \qquad \textbf{(2)}$$

where $C(t)$ is relative concentration at time t, C_o is acetone initial concentration which was normalized to unity, and finally τ is the mean residence time of the reactor. Experimentally, pure heptane was transferred to CSTR via a piston pump at rate of 10 mL/min for a mean residence time, τ, of 10 min. The liquid from the reservoir was added directly under the agitator at 300 RPM to enhance mixing. Figure 12 presents a comparison of acetone relative concentration experimentally measured by FTIR versus that predicted by Equation 2 assuming an ideal CSTR. The excellent agreement between the two profiles suggests that the new reactor closely resembles an ideal CSTR and that behavior associated with channeling and/or dead volumes was not observed.

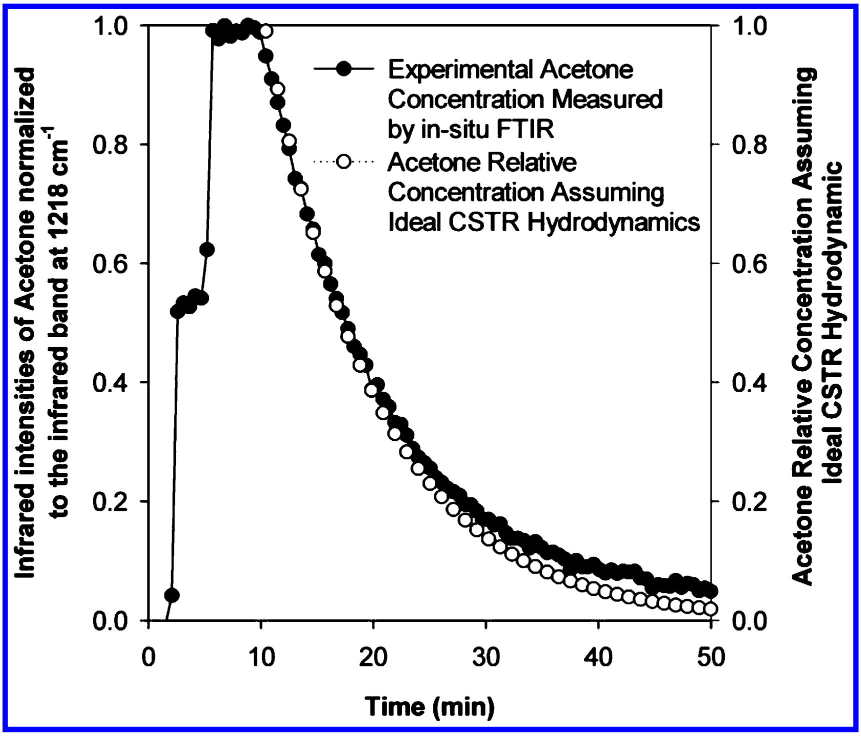


Figure 12. Acetone Relative Concentration (●) Experimentally Measured by FTIR and (○) Predicted Assuming Ideal CSTR RTD. (Reproduced with permission from reference (34) (2011) American Chemical Society)

Besides confirming ideal CSTR, the concentration profile in Figure 12 can also shed light on the general use of CSTR for continuous processing. Equation 1 indicates that if we operated the CSTR at relative residence time of 10 min, 10% of the incoming material will spend less than 1 min in the reactor. On the other hand, 5% of the incoming stream will spend 30 min or more inside the CSTR. This wide range of residence time proved inconsequential to ozonolysis due to fast kinetics and lack of any over-oxidation impurities. This conclusion is substrate specific and cant be generalized. Nevertheless, the use of CSTR should be examined thoroughly before adapting it to other reactions. Particularly for reactions that are slower and thus portions of the entering substrate that has short residence time will not have sufficient time to react. Furthermore, readers should be aware that in some scenarios prolonged exposure of product to reaction condition can lead to degradation and impurity formation. Under these scenarios CSTR might not be the best tool and actually PFR will be more appropriate.

Exploring Ozonolysis in the CSTR Using Styrene as Model Compound

After ensuring ideal CSTR behavior using RTD analysis, and the absence of both channeling and dead zones, the retrofitted reactor was used for the model ozonolysis of styrene in continuous mode. The concentration was deliberately chosen so that the flow rate of the styrene molar flow will be equimolar to ozone supply: 2.3 mmol/min. Again, an FTIR probe was used to monitor the concentration profile in CSTR. A third quench reactor was attached to the overflow valve. A schematic diagram of the setup is shown in Figure 13.

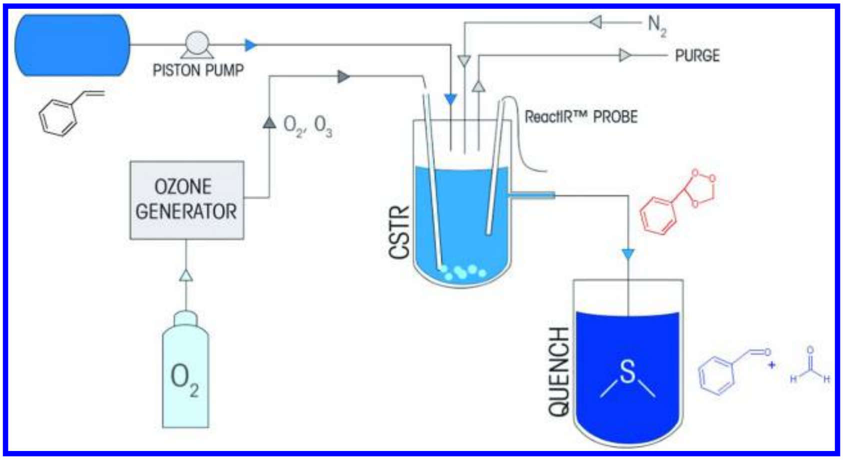


Figure 13. Schematic Diagram of the CSTR Setup used for Continuous Ozonolysis of Styrene. (Image courtesy of Mettler Toledo (35))

The temperature of the CSTR and quench tank was set to -50 °C and -1 °C, respectively. The ozone supply from the ozone generator was connected to the CSTR in the same manner as in the semi-batch run, i.e. gas bubbles released under the mixing blades. Initially, 200 mL of the reservoir solution (46 mmol styrene) was transferred to the CSTR, and then the observed FTIR intensity at 780 cm^{-1} was used to deduce number of moles of styrene inside the CSTR (Figure 14).

With the pump feeding the CSTR turned off (flow 0 mL/min) and reactor overflow valve to the quench tank closed, the CSTR was effectively operated in semi-batch mode. The ozone generator was turned on and gas was allowed to bubble in the CSTR. After 40 min (i.e. 21 min after introducing ozone) styrene (46 mmoles) was completely consumed. The rate of reaction was linear and about 2.2 mmol/min, in excellent agreement with results obtained during the semi-batch experiments in the previous section. During ozone addition, despite maintaining the jacket temperature at -50 °C, the reactor temperature rose from -50 °C to -38 °C due to reaction exothermicity.

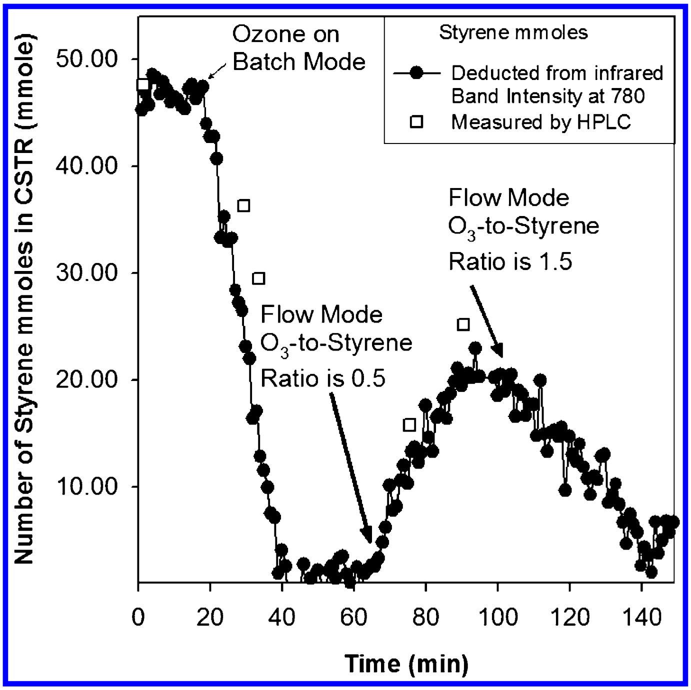


Figure 14. Number of Styrene mmole in the CSTR (●) Deducted from FTIR Intensity at 718 cm^{-1} (□) Measured by Off-line HPLC. (Reproduced with permission from reference (34) (2011) American Chemical Society.)

Next, the setup was operated in continuous mode by setting the pump feeding the CSTR from the reservoir solution to 15 mL/min i.e. 3.5 mmol/min of styrene (50% excess styrene with respect to ozone). In addition, the overflow valve was opened in order to allow excess liquid to overflow into the quench tank. With an insufficient amount of ozone, styrene accumulated inside the CSTR to half of its original concentration, as expected to 50% molar excess of the substrate feed which provides strong evidence of ideal CSTR behavior and the high efficiency of ozone absorption. The flow rate from the reservoir was reduced to 5 mL/min making ozone-to-substrate molar ratio 1.5. In presence of excess ozone, the number of moles of styrene dropped, as expected. The in-situ FTIR capability to quantitatively monitor styrene was validated by several off-line HPLC measurements (Figure 14).

Ozonolysis of the Substrate of Interest 9 in the CSTR

The same CSTR setup used for the model ozonolysis of styrene was now employed for the ozonolysis of our substrate of interest **9** (Scheme 5). Despite the fact that the setup was very efficient in ozone absorption during styrene ozonolysis, a ratio of about 1.2 ozone-to-substrate was used to ensure 100% conversion. The setup was operated in continuous mode in 12 h shifts for four days, generating ~90 g/day. The batches were combined and displayed 98% conversion. Approximately 300 g of product was generated (81% isolated yield) after workup.

Scaling up ozonolysis in batch mode for the same scale would have required a larger reactor vessel which has a smaller surface-to-volume ratio and thus less efficiency in removing heat. Consequently, a batch mode process would dictate lowering the ozone supply to maintain low temperature and thus would require a longer cycle time as compared to our continuous approach. Furthermore, carrying out the reaction in batch mode would require the conversion of all starting material to ozonide prior to the quench, potentially accumulating 100% of the unstable ozonide (2880 mmol). Operating in flow mode using the current CSTR kept ozonide inventory to less than 46 mmol at any given time, a far safer operation.

Ozonolysis in a Continuous Bubble Reactor

Shortly after successfully delivering the required aldehyde product using the CSTR, a new clinical need for an additional 2.5 kg of product arose. The lab scale ozone generator throughput was too small to meet the demand. Therefore, in order to increase the scale of the continuous ozonolysis reaction, a larger ozone generator, capable of producing 150 mol/min of O_3 was employed. The minimum total gas flow rate of the larger ozone generator was 17 L/min, compared to a 2 L/min flow rate in the lab scale ozone generator. Attempts to bubble the gas stream using a subsurface tube next to the blades as used in the previous batch and CSTR reactors were not feasible as the gas flow rate was very high and entrained significant amounts of solvent upon exiting the vessel. There was a need to investigate different reactors geometries that can handle such higher gas flow rates.

Continuous Bubble Reactor Fabrication

Our team set its vision on developing a reactor system capable of dealing with the higher gas volume rate. The new apparatus needed to allow continuous operations and provide good mass transfer from the gas phase (ozone) to the liquid phase. This prompted us to develop a 2 L continuous bubble reactor (CBR) as an alternative to the retrofitted CSTR. The setup was internally designed and constructed to accommodate high gas flow rates. In addition, the designed bubble column allowed continuous operation, ease of cleaning, and the use of PAT (Figure 15).

The reactor was jacketed for temperature control and had a large diameter coarse frit at the bottom in order to introduce a high gas flow rate with minimal pressure drop. Furthermore, the frit allowed for the production of fine gas bubbles from the incoming gas stream and thus enhanced gas-liquid mass transfer. The high velocity gas further resulted in enhanced mixing of the liquid phase inside the bubble reactor so its hydrodynamic profile is expected to follow that of an ideal CSTR. Three valves were connected to the side of the CBR reactor. The bottom valve is predominately for drainage and cleaning purposes. The other two valves function as overflow valves to allow continuous operation at various constant volume levels.

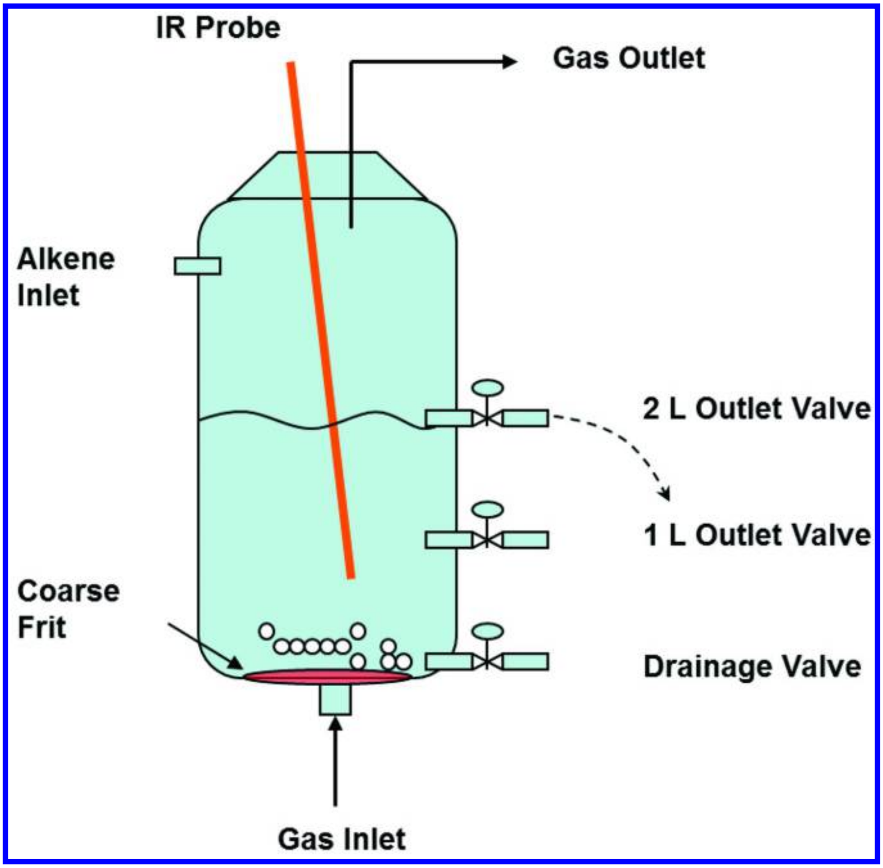


Figure 15. Schematic Diagram of the in-house Designed Continuous Bubble Reactor. (Reproduced with permission from reference (34) (2011) American Chemical Society.)

Continuous Bubble Reactor Evaluation with Styrene as Model Compound

The efficiency of the new continuous bubble reactor (CBR) in absorbing ozone at these high gas flow rates and the feasibility of operating the bubble reactor in continuous mode were evaluated using the model substrate styrene. Styrene in methanol was transferred to the CBR and temperature was set to -33 °C (lowest temperature attainable). After substrate solution transfer, the pump was turned off and the rate of ozonolysis was studied in a batch mode using in-situ IR. Next, the outlet of the new ozone generator was connect to the bottom of the CBR and was operated with air as a feed gas and appropriate settings that would generate 11 mmol/min of ozone. Upon introducing ozone, the number of moles of styrene dropped linearly at a rate of 9 mmol/min until completion (Figure 16).

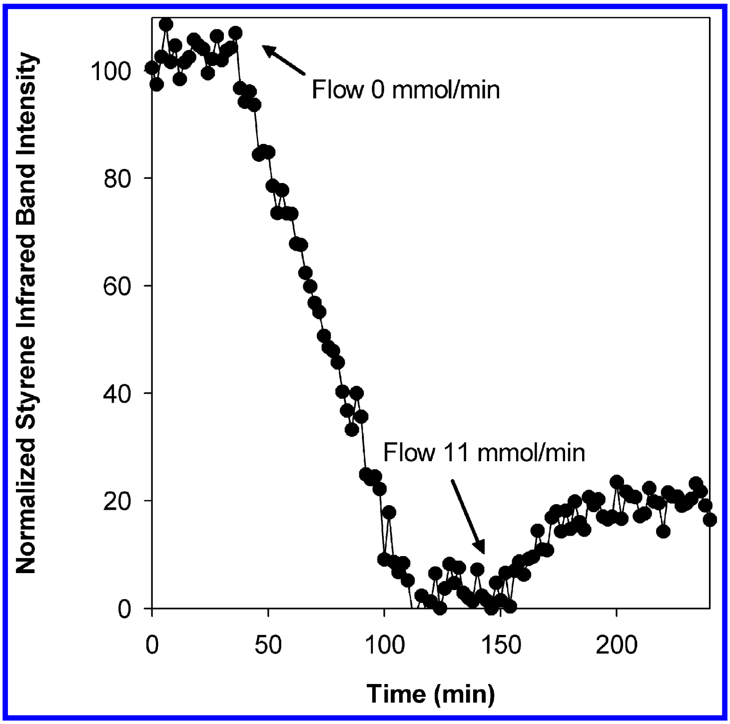


Figure 16. Normalized Styrene Concentration Based on FTIR Band Intensity inside Continuous Bubble Reactor. (Reproduced with permission from reference (34) (2011) American Chemical Society.)

During batch mode operation, the initial amount of styrene inside the CBR is 84 g (810 mmol) and at the current ozone feed of 11 mmol/min, the duration of the styrene consumption should have been 75 min assuming 100% efficiency in ozone absorption. The extra time, 88 min rather than 75 min, indicates that the custom designed CBR allowed 85% efficiency in ozone absorption. In other words, the new CBR is reasonably efficient in terms of ozone absorption despite the high gas flow rate. The reactor jacket temperature was maintained at -33 °C, however during the course of reaction the reactors temperature increased from -33 °C to -12 °C due to reaction exothermicity. The -12 °C point was still well below the observed decomposition onset temperature of 42 °C observed for the reaction mixture by DSC. The team did not attempt to operate at temperatures higher than -10 °C as this can reduce ozone solubility and thus CBR efficiency in absorbing ozone would be reduced.

Next, continuous operation was initiated by adding styrene to the CBR at a rate of 11 mmol/min and opening the 2-L overflow valve to allow excess reaction mixture to overflow to the quench tank. As the CBR is ~85% efficient in ozone absorption, gradual increase in the concentration of unreacted styrene is expected. Indeed, at 150 min in continuous mode, un-reacted styrene concentration increased gradually until reaching a steady state of about 20% indicating that ozone supply was not sufficient (Figure 16).

Ozonolysis of the Substrate of Interest 9 in the Continuous Bubble Reactor

Next we employed the continuous bubble reactor (Figure 17) to carry out the ozonolysis of our substrate (Scheme 5). Two key results from styrene ozonolysis were used in designing the delivery run at the pilot plant, namely that an ozone-to-substrate ratio of 1.3 is needed to compensate for the CBR inefficiency of 15%. Second, the current setup throughput is 80 g/h with respect to our substrate, therefore in order to accommodate the 10 hr shift the 2.5 kg delivery was split into four batches.

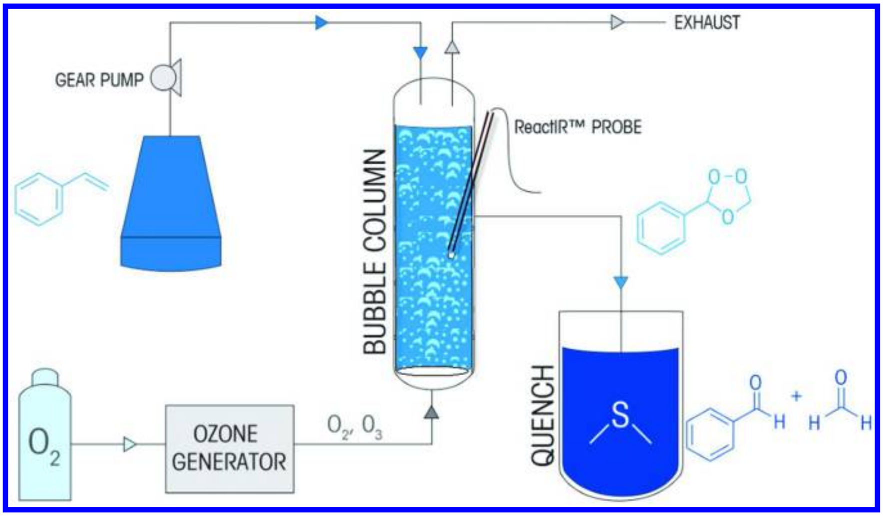


Figure 17. Schematic Diagram of the CBR Setup used for Continuous Ozonolysis of Styrene or Substrate ***9****. (Image courtesy of Mettler Toledo (35))*

The startup of the process include preparing the starting material solution feed tank. Afterward, the quench solution of DMS was also prepared. Then, 1 L from reservoir solution was transferred to the CBR. Although the CBR can be operated with either 1 L or 2 L, the 1 L setting was selected because weve encountered significant foaming while bubbling gas into the solution and operating at 1 L volume ensured that no foam reached the head space of the reactor. We employed two ozone detectors with built in alarms both inside and outside the fumehood. Interestingly, the detector inside the fumehood, placed near CBR exhaust, turned into a very powerful PAT tool in addition to the in-situ IR (vida infra). The reactor jacket temperature was maintained at -33 °C throughout the process.

After transferring the 1 L solution of the starting material, the pump was turned off and CBR was operated in a batch mode. The ozone generator was turned on and concentration of the alkene intermediate was monitored by in-situ IR. During the course of ozone addition, the reactor temperature increased from -33 °C to -12 °C due to reaction exothermicity. However, when the substrate was consumed, the reactor temperature started dropping again. The time needed to consume the substrate, based on IR data, was in excellent agreement with what we predicted. Another indication that substrate was consumed was that the ozone detector alarm inside the fumehood was triggered due the higher level of ozone escaping the reactor. Minutes later, the solution inside the CBR turned blue indicating the solution was saturated with ozone. At this point, the outlet of the CBR was opened to allow ozonide solution to flow to the quench and we immediately started metering in the alkene solution.

There is no recovery pathway for the unreacted alkene substrate that makes it to the quench tank. Furthermore, this was not just a yield issue because the unreacted started material posed challenges during downstream purification. Therefore, the team and the operators must ensure that sufficient ozone is supplied to the reactor and were instructed that if substrate concentration started to build up in the CBR that they immediately halt substrate addition. We kept a close eye on the in-situ IR signal and at the ozone levels in the fume hood. On two separate occasions, the process was stopped because the IR signals have detected buildup of alkene starting material in the CBR. The increase in starting material is due to either over-charging the substrate or undercharging ozone. The latter possibility can be eliminated because the alkene solution was on a scale and the flow rate was very well controlled. We quickly realized the reason for buildup of substrate was the fact that ozone generator output was not stable and over time its throughput was dropping. Increasing the power can quickly increase the amount of ozone input and remedy the situation. Despite, these minimal operational challenges, 99% conversion of starting material was achieved. Solutions from all four runs were combined and processed successfully to make the 2.5 Kg delivery. Inside the CBR, the number of moles of ozonide at maximum is ~ 950 mmol, compared to potentially ~ 24000 mmol if the reaction was operated in batch mode to obtain the same amount of product. In other words, the CBR significantly reduced the hazard associated with the reaction and also allowed better temperature control by operating in smaller reactors. Furthermore, the new CBR allowed excellent gas-liquid mass transfer despite the higher gas flow rate from the new ozone generator.

Experimental Details

Experiments were conducted on various scales, ranging from 100-5000 mL using Chemglass jacketed glass vessels equipped with overhead agitators (retreat curve) and K-type thermocouple for temperature measurements. The description of the thermal analysis carried out along with a representative experiment in each of the setups is discussed in this section.

Reaction Calorimetry (RC1)

A solution of our terminal alkene drug intermediate [9] (5 g), dichloromethane (65 g) and methanol (8 g) were charged into the 80 mL RC1 reactor. The reactor was equipped with a turbine agitator and was cooled to -45 °C. After calibration, the outlet line of the ozone generator was bubbled into the reactor for ~ 70 min. After ~ 60 min, the solution turned blue. After turning off the ozone generator and calibration, the reactor contents were slowly heated to 0 °C over 45 min. After stabilization and calibration, DMS was added via pressure transfer over 20 min. After stabilization and calibration, the test was concluded. Based on calibration, the average heat capacity $C_{p,r}$ and the overall heat transfer coefficient for the reactor U_A were 1.25 J/K/g and 1.38 W/K respectively.

Kinetics in Batch Mode

A solution of methanol (200 mL) was cooled to -50 °C and a spectrum of the solvent was recorded using an FTIR fiber optic probe (ReactIR IC10- Mettler Toledo) immersed in the liquid phase. Styrene (6 mL) was added to the reactor in two portions and several spectra (5-10) recorded after each addition. The addition of styrene to methanol at -50 °C resulted in an infrared band at 780 cm^{-1}. When an equal amount of styrene was added, the band approximately doubled (Figure 8). For the semi-batch experiments, a lab scale ozone generator (Polymetric, Inc.) was used with the settings of 90 V and 8 psi of O_2 pressure and gas flow of 2 L/min. According to the ozone generator manual, these conditions result in converting 2.76% of the oxygen flow into ozone or 6.5 g/h (2.3 mmol/min) of ozone. Ozone was introduced to the reactor under the impellers blades in order to enhance mass transfer until complete consumption of the styrene was evident by FTIR. The ozone was turned off along with the chiller allowing the reactor to warm up to room temperature on its own. Then, the reactor contents were quenched by adding DMS until less than 1 ppm peroxide was present using J.T. Baker “Testrips for Peroxide”.

Continuous Stirred Tank Reactor Mode (CSTR)

The reservoir tank was prepared by mixing 30 g styrene in 1.2 L methanol. The quench reactor was attached to the overflow valve and was charged with 500 mL methanol and 19 g of DMS. The CSTR jacket temperature was set to -50 °C while the quench solution was cooled to -1 °C under nitrogen. Methanol (200 mL) was transferred to the CSTR via a piston pump. Collection of FTIR spectra of CSTR content was initiated. Ozone was introduced until complete consumption of the styrene was evident by FTIR. The setup was operated in continuous mode by setting the pump at an appropriate flow rate and opening the overflow valve in order to allow excess liquid to overflow into the quench tank. At the end of the experiment, ozone was turned off, the content of the CSTR was drained and manually added to the quench pot. Then, DMS was added to the quench until less than 1 ppm peroxide is present with J.T. Baker “Testrips for Peroxide”.

Continuous Bubble Reactor Mode (CBR)

The styrene reservoir was prepared by mixing 300 g of styrene with 5 L of methanol. The styrene reservoir was transferred to the CBR via a Teflon gear pump. FTIR spectra began to be recorded from inside the bubble reactor. The 2 L valve at the bubble column reactor was connected to the quench tank whose temperature was set to ~0 °C. The 10 L quench reactor contained 500 mL methanol and 257 mL DMS. The ozone generator was operated with air as a feed gas at 17 L/min, 2.5 bar pressure and using 0.5 kW power. According to the manual, these conditions generate 31 g/hr of ozone which correspond to 11 mmol/min. The outlet of the ozone generator was connected to the bottom of the bubble reactor. The reactor was operated in batch mode until styrene consumption in the CBR was complete. Then continuous operation was initiated by turning on the pump to 16 g/min and opening the 2 L side valve on the CBR to allow excess volume to flow into the quench tank. At the end of the experiment, ozone was turned off and the content of the CBR was drained into the quench tank via the bottom valve of the CBR. Finally, DMS was added to the quench until less than 1 ppm peroxide is present with J.T. Baker "Testrips for Peroxide".

Acknowledgments

The author is grateful to Steve M. Richter (process safety lab) for constant feedback and conducting the calorimetric tests. I also would like to thank Jeffrey M. Kallemeyn and Vimal Kishore for helpful discussions. Tim Robbins and his team supported the transfer of this nontraditional reaction process from lab to the plant and their contribution was instrumental to the success of this initiative.

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38. For a gram of substrate, ΔH_{net}=4785 J, m_{total} =15.6 g and $C_{p,r}$ =1.42 J g^{-1}K^{-1}.

Chapter 14

Development of Flow Processes for the Syntheses of *N*-Aryl Pyrazoles and Diethyl Cyclopropane-*cis*-1,2-dicarboxylate

Bryan Li[*] and Steven Guinness

Chemical Research & Development, Pfizer Worldwide Research & Development, Eastern Point Road, Groton, Connecticut 06340, USA
[*]E-mail: Bryan.li@pfizer.com

Part 1: N-Aryl pyrazoles were prepared from anilines in a three step telescoped approach. An aniline was diazotized to give the diazonium fluoroborate, followed by reduction with tin(II) chloride to give the corresponding hydrazine, which in turn reacted with a ketoenamine to give the *N*-aryl pyrazole. The deprotection of the methyl ether was accomplished with $PhBCl_2$ to give the final product. Continuous flow methodology was used to minimize accumulation of the highly energetic and potentially explosive diazonium salt and hydrazine intermediates to enable safe scale-up. The heterogeneous reaction mixture was successfully handled in both lab scale and production scale. A continuous extraction was employed to remove organic impurities from the diazotization step, which eliminated the need for chromatography in the purification of the final *N*-aryl pyrazole.

Part 2: A continuous stirred tank reactor (CSTR) flow process for the preparation of diethyl cyclopropane-*cis*-1,2-dicarboxylate involved the use of lithium hydride powder is described. Batch reaction kinetics were established and used to design the CSTR. The solid/liquid heterogeneous reaction mixture using lithium hydride with generation of highly flammable hydrogen gas was successfully managed at multi-hundred gram scale in laboratory production. The observed conversion rate was essentially the same as predicted from the design equation for the two equally sized reactors,

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though the *cis/trans* ratio was slightly lower than from the batch process. The demonstration of the CSTR flow process made it possible to obtain diethyl cyclopropane-*cis*-1,2-dicarboxylate on larger scales.

1. A Telescoped Flow Process for the Syntheses of *N*-Aryl Pyrazoles

The pyrazole moiety is a key pharmacophore in many pharmaceutically active agents. Naturally occurring Pyrazofurin (**1**), a *C*-nucleoside isolated from *Streptomyces candidus* in 1969, possessed broad-spectrum antiviral activity (*1*, *2*). Multiple blockbuster drugs celecoxib (**2**, Celebrex®), rimonabant (**3**, Acomplia®), sildenafil (**4**, Viagra®) and the lung cancer drug crizotinib (**5**, Xalkori®) all feature a pyrazole substructure (Figure 1).

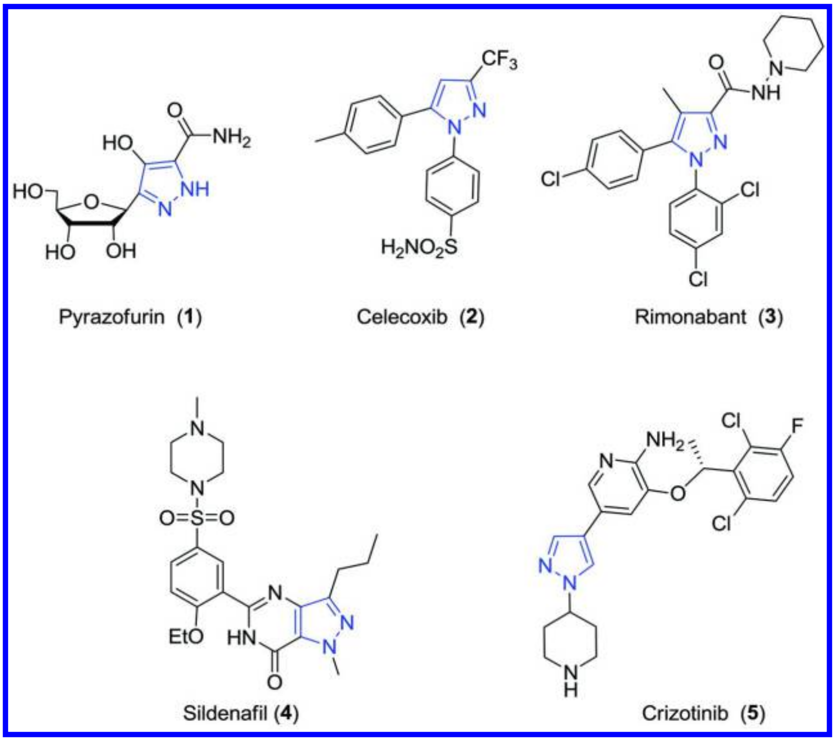
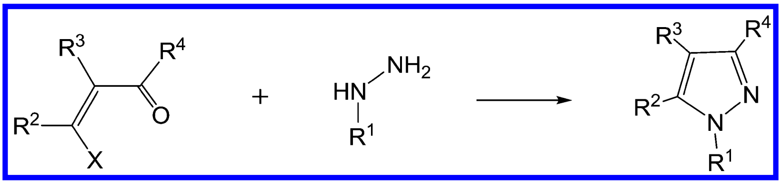

Pyrazofurin (**1**)
Celecoxib (**2**)
Rimonabant (**3**)
Sildenafil (**4**)
Crizotinib (**5**)

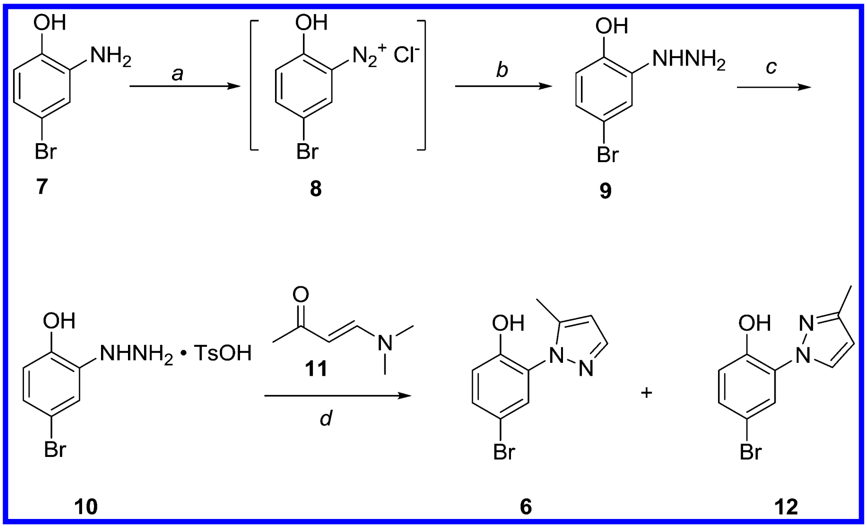
Figure 1. Some drugs containing a pyrazole moiety

A number of synthetic methods have been developed for the formation of pyrazoles (*3*, *4*). Among them, the Knorr (*5*) cyclocondensation offers direct entry to the pyrazole via cyclocondensation of hydrazines with 1,3-dicarbonyl compounds or their surrogates (Scheme 1). The commercial availability of ketoenamines, RC(O)CH=CHNMe$_2$ (R = H, Me, Ph, OEt) and the accessibility of hydrazines make the Knorr reaction one of the most attractive methods for the preparation of pyrazoles. Importantly, when the nitrogen groups of hydrazines are electronically or sterically biased, reasonable regioselectivity can be achieved in the pyrazole formation (*6*).



Scheme 1. Knorr Cyclocondensation

We adopted such approach in the synthesis of *N*-aryl pyrazole **6**, a key intermediate for an ongoing research program (Scheme 2). The synthesis started with diazotization of 2-amino-4-bromophenol (**7**), followed by reduction of the diazonium salt **8** to give the hydrazine **9**. The isolation of **9** was complicated by the presence of tin oxides in the reaction mixture. After cumbersome extractive workup, crude **9** was isolated and purified by forming the tosylate salt (**10**). Subsequently, **10** was reacted with ketoenamine **11** to give the aryl pyrazole **6**. The regioisomer **12** (8-10% by HPLC) was formed as a byproduct and was removed by silica gel chromatography. While the synthesis was relatively straightforward on small scale, the involvement of low Differential Scanning Calorimetry (DSC) onset temperature energetic intermediates, diazonium salt 8 (DSC onset 123°C, ΔH -614 J/g) and hydrazine **9** (DSC onset 82°C, ΔH -670 J/g), presented potential safety hazards for scale-up.



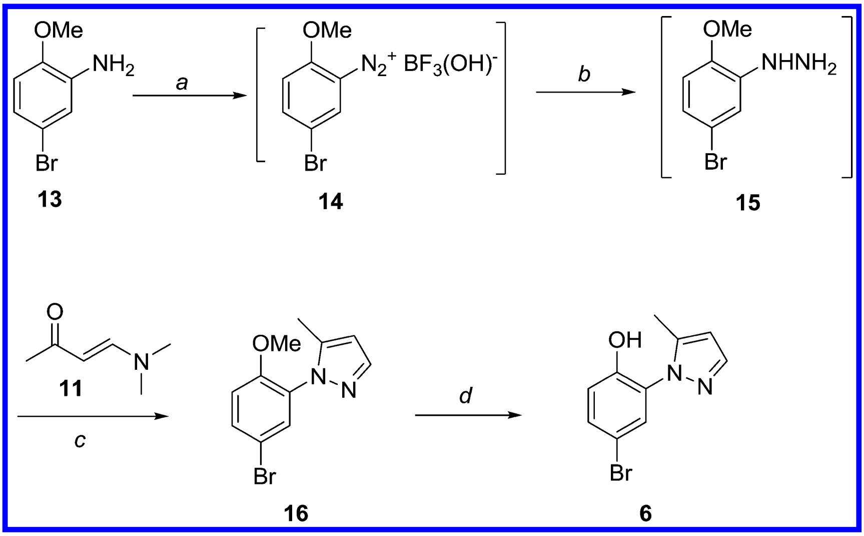
Scheme 2. Medicinal Chemistry Synthesis of N-Aryl Pyrazole **6**. *(a) NaNO*$_2$*, aq. HCl, 0 °C. (b) SnCl*$_2$*, EtOH, AcOH, 0°C to RT; then extractive workup, (c). TsOH•H*$_2$*O; (d) AcOH, RT.*

We turned our attention to developing a continuous flow process to address the safety concerns in scale-up. Continuous flow technology offers many advantages over batch methods including precise control of stoichiometry, reaction time and temperature, high reproducibility, and often better reaction yields (*7–13*). The much higher surface area to volume ratio under flow conditions renders highly efficient heat transfer. When coupled with the much smaller volume in the reaction train, safety hazards in handling exothermic reactions associated with explosive intermediates are minimized (*14–17*).

1.1. Adapting the Batch Chemistry to Continuous Flow

As an industrial process of vast importance, the diazotization of aromatic amines has been well studied (*18*). A continuous diazotization of anilines was reported in 1965 from the dye industry (*19*). More recently, there have been several reports on generating diazonium salts as reactive intermediates using flow technology (*20–22*). In the design of a continuous flow process for the synthesis of **6**, our objectives were to avoid the accumulation and isolation of both energetic intermediates **8** and **9**. We envisioned that appropriate reaction conditions in a telescoped process would satisfy these objectives. Thus, we set to enable reaction conditions for each transformation and explore telescoping opportunities. As expected, the diazotization of aniline **7** worked well under either aqueous ($NaNO_2$, aq. HCl) or non-aqueous (*t*-BuONO, BF_3•THF) (*23*) conditions. Though it was highly desirable to eliminate $SnCl_2$ from the synthesis, our efforts to find alternative reducing agents to replace $SnCl_2$ were fruitless (*24–26*). When crude diazonium **8** was carried to the $SnCl_2$ reduction, it failed to convert cleanly due to the presence of a number of impurities generated from the diazotization. This profile led to low overall yields when the hydrazine reaction mixture was subjected to the pyrazole formation. The use of $SnCl_2$ also complicated the work-up and isolation as a large amount of tin oxide by-products gave a milky mixture. Tin oxides are only soluble in either highly acidic or basic aqueous media that were not suitable for the isolation of zwitterionic **9** or **6**. With that in mind, we turned to the methyl ether protected analog aniline **13** (less expensive than **7**) as the starting material (Scheme 3). It offered a cleaner reduction step, and resulted in a much more convenient isolation of hydrazine **15** or pyrazole **16**, as high pH conditions that solubilized tin oxides could be applied during the work-up.

To streamline the process, we next examined if ketoenamine **11** was stable in $SnCl_2$ (1 equiv)/EtOH, and were pleased to observe no appreciable degradation at 20 °C over 24 h. Since reaction rates for the diazonium reduction and the cyclocondensation steps occurred within minutes, neither energetic intermediates **14** (DSC onset 123 °C, ΔH -424 J/g) and **15** (DSC onset 105 °C, ΔH -602 J/g) would be accumulated in a telescoped process.



Scheme 3. New Synthesis of N-Aryl Pyrazole ***6****. (a) t-BuONO, BF_3•THF in 2-MeTHF; RT. (b) $SnCl_2$, 2-MeTHF/water, 0°C. (c) 0 – 20 °C. (d) $PhBCl_2$, toluene, 95°C, 3 h; recrystallization in iPrOH/water.*

1.2. First Generation Flow Design

Since the diazonium intermediate **14** was observed to react further with the aniline starting material to give azo coupling by-products, we wanted to avoid back mixing in a flow reactor. Thus, a plug flow design was selected (Figure 2) instead of a continuous stirred tank reactor (CSTR). Aniline **13** was combined with BF_3•THF in THF as one feed stream. The resulting solution was evaluated for its stability, and revealed no concerns over 24 h. *t*-Butyl nitrite in THF was introduced as a separate stream. The two streams were pumped into a T-mixer followed by a PTFE coil to achieve a 10 min residence time for the diazotization reaction. The coil was submerged in a sonication (*27*) bath to allow the diazonium salt formed in the coil to move smoothly out of the PTFE coil without clogging. Crystallization of diazonium fluoroborate salt (**14**) in the reaction mixture resulted in a systemic pressure of 30 – 45 psi. It was noted that **14**, as a light and fluffy solid, was well suspended in THF and was unlikely to lead to clogging. The effluent was directly added to a receiving flask containing $SnCl_2$ and ketoenamine **11** in ethanol. This design worked successfully up to 100 g scale and gave confidence that further scale up would be successful. After an extractive workup, pyrazole **16** was isolated by chromatography, and underwent methyl ether deprotection using $PhBCl_2$ (*28*) to give the desired product **6** in 35 – 40% overall yield.

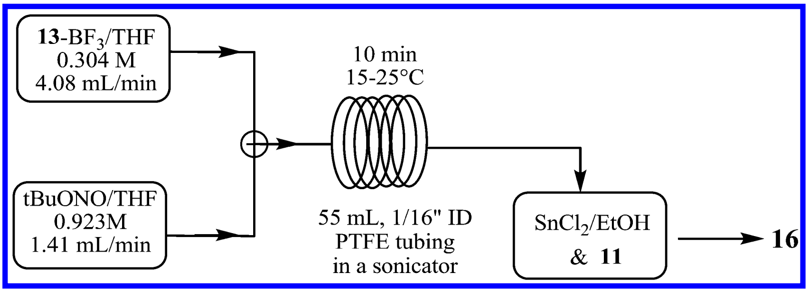


Figure 2. First generation flow set-up

1.3. Second Generation Flow Design

While the first generation flow design allowed the successful scale up to meet the initial demands, isolation of the final product still required silica gel chromatography. As the program progressed, larger quantities of **6** were demanded, and it became evident a more efficient synthesis was needed. Since most impurities (*29*) from the 3-step sequence were generated in the diazotization step, and an excess of *t*-butyl nitrite was found to give rise to high levels of impurities in the reduction, we envisioned an opportunity to introduce a continuous extraction to allow the separation of the water-soluble diazonium salt **13** from the organic-soluble impurities. This idea was demonstrated by purifying a small amount of **13** and carrying it forward to **16** with high purity and good yield, leading to the second generation flow design (Figure 3).

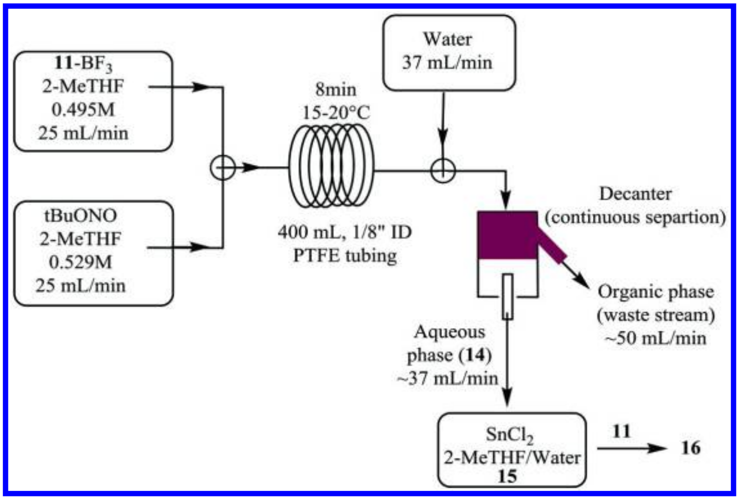


Figure 3. Second generation flow set-up

The flow set-up used two Fluid Metering Inc. (FMI) pumps (with the mechanism of valveless rotating and reciprocating piston metering) to introduce the feed streams. A stainless steel T-union was used as a mixer, which was joined by PTFE tubing to provide the required residence time. Considering the upper pressure limit of the pumps is 100 psi, we used an automatic pressure shut-down device with a trigger point set at 100 psi. The effluent (out of the PTFE tubing) from the diazotization reaction was mixed with a water stream using a two staged continuous stirred tank reactor (CSTR), the resulting biphasic mixture then entered a glass standpipe decanter (Figure 4) for phase separation. The organic layer was continuously removed as a waste stream, while the aqueous phase was directed into a reaction vessel containing $SnCl_2$.

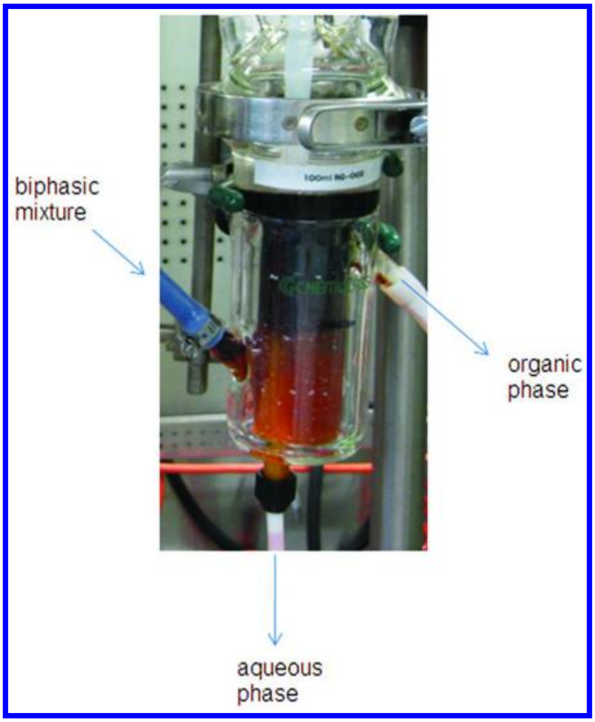


Figure 4. A real time picture taken for the continuous extraction in the 2nd generation flow design (30). – Reproduced with permission from reference (30). Copyright (2012) American Chemical Society, Washington, D. C.

Some modifications of the chemistry were required to enable this new design. In order to facilitate the continuous extraction, the diazotization solvent was changed to 2-MeTHF to accelerate separation from the aqueous layer. We also determined that the residence time could be reduced from 10 min to 8 min. Secondly, the $SnCl_2$ pot receiver was held at 0-5 °C during the reduction which resulted in a better purity profile, and ethanol was eliminated for more streamlined workup and isolation. Third, with water introduced to the system, the aqueous hydrazine intermediate presented a low hazard in thermal stability testing and it was deemed safe to accumulate hydrazine **15** in a solvent mixture of water/2-MeTHF (tested using a Thermal Screening Unit or TSU; reaction stability test showed neither thermal nor gas onsets held at 60 °C). Ketoenamine **11** was added after the flow run was complete and the mixture was then warmed to 20 °C for a cleaner reaction. Using this protocol, we executed 2 runs (800-1000 g), and obtained 51–55% overall yield of **6**. With flow rates of 25 mL/min for both the BF_3-aniline adduct and *t*-butyl nitrite feed stream solutions, a back pressure of ~30 psi resulted due to the diazonium solids present in the PTFE tubing. A picture of the 400 mL reaction coil used in the production run is shown in Figure 5. After approximately 3 min of residence time, the diazonium salt started to crystallize from the reaction mixture, however the solids were light and fluffy and moved through the coil smoothly. Liquid segments were noted as the solid segregated in mother liquor from the crystallization. The FMI pumps were able to handle the slurry formed in the 400 mL PTFE tubing (1/8” ID, 1/4” OD, rated to handle 320 psi of pressure @ 23°C) in a continuous ~8 h operation. It is plausible that the pulsating effect generated from the FMI pumps might have helped in moving the slurry. A process hazard analysis (PHA) was conducted and the following was recommended and followed:

- The whole system was tested to ensure to withstand up to 250 psi pressure with no leaks detected. All tubing and fittings used should be rated for much higher pressure at the operating temperature (This requirement was readily satisfied with the use of PTFE tubing and SwageLok® fittings).
- Each run should be closely monitored despite the implementation of an automatic shut down device at 100 psi.
- In the event of pressure buildup due to solid agglomeration, the coil containing the diazonium intermediate was to be flushed with water immediately and kept from exposure to air.

Fortunately we did not need to use the contingency plan in the kilogram scale flow run.

It is noteworthy that the continuous separation worked extremely well for the chemistry. The standpipe decanter vessel (100 mL) could accommodate flow rates of 120 mL/min per stream with facile layer separation. The emulsion zone between the phases was approx. 10 mm out of the total height of ~140 mm of the biphasic layers during the course of both flow runs (Figure 4).

With crude **16** in hand, we sought an efficient work-up and isolation method. Upon complete conversion of the hydrazine **15** to the pyrazole **16**, the aqueous phase was removed, and the organic phase was washed with 6N aq. NaOH. The mixture was filtered, and the filtrate was concentrated and treated with silica gel. This method effectively reduced the residual tin level to <10 ppm.

The crude product was then subjected to demethylation using $PhBCl_2$ (*28*) in toluene. Finally, a crystallization method was developed to remove the regioisomer **12** using a mixture of isopropanol and water.

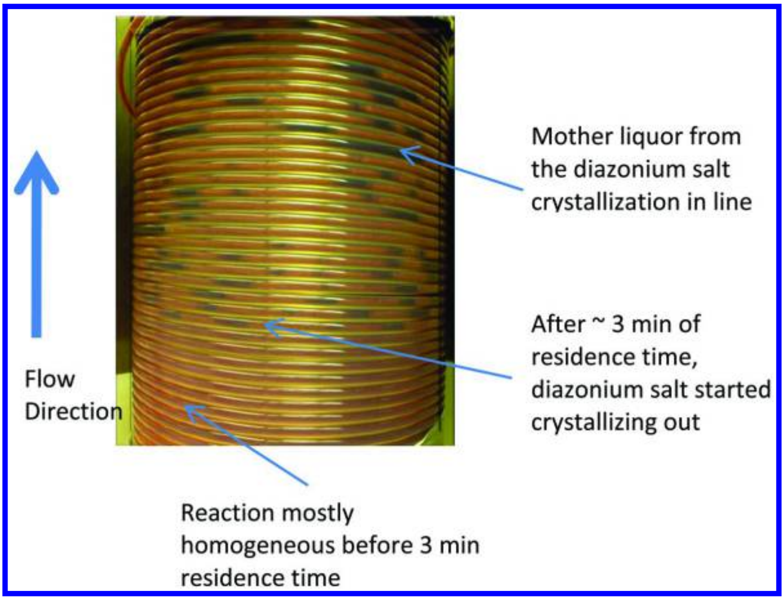


Figure 5. Diazonium fluoroborate salt crystallization in the reaction coil (1/8" ID, PTFE, 400 mL). – Reproduced with permission from reference (30). Copyright (2012) American Chemical Society, Washington, D. C.

1.4. Summary

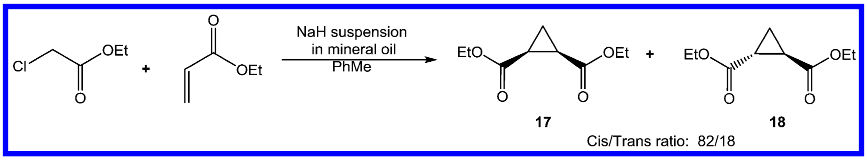
We have described a flow process allowing the safe handling of the energetic intermediates to our target pyrazole. The maximum amount of diazonium salt **14** present in the system was 99 mmol (29.6 g, assuming 100% conversion) for the scale up using 400 mL coil. For comparison, a batch reaction of 1.0 kg scale would generate 4.9 mol of diazonium salt **14**. Under the worst case scenario of decomposition of all diazonium salt in the reaction system, approximately 2.2 L of nitrogen (under 1 atm pressure) would be generated in the continuous production scale. Whereas the batch reaction would generate 110 L of nitrogen upon decomposition.

In the diazotization step, while the feed streams were homogeneous solutions in the flow operation, the product stream became a slurry after ~3 min of residence time. The solid/liquid heterogeneous reaction mixture (5 – 7 wt% solids) was successfully handled at kilogram scale production scale (400 mL PTFE 1/8" ID coil) without sonication. The continuous extraction employing a simple stand pipe decanter effectively removed organic-soluble impurities from the diazonium salt (**14**), which also resulted in higher throughput in the three step telescoped process.

Despite the successful outcome of the flow runs demonstrated in the preparation of *N*-aryl pyrozole **6**, the robustness of the process on any scale larger than 1 kg of **13** and longer duration is yet to be tested. We plan to further investigate the flow design if the need arises for greater demand of the aryl pyrazole **6**. Additionally process improvements on the product isolation and the demethylation step will also be necessary.

2. Preparation of Diethyl Cyclopropane-*cis*-1,2-dicarboxylate by CSTR Flow

The synthesis of diethyl cyclopropane-*cis*-1,2-dicarboxylate (**17,** Scheme 4) is well precedented in the literature (*31*, *32*), and seems a simple task. Multi-grams of the material can be obtained in the laboratory by exercising careful control of addition rate and bath temperature. Nevertheless it was not a complete surprise that no quotes were returned from vendors because of safety concerns for handling NaH and forming energetic cyclopropane intermediates when multi-kilograms of the material were requested.



Scheme 4. Synthesis of Diethyl Cyclopropane-cis-1,2-dicarboxylate

With the need to move the project forward, we took a closer look at the reaction. Other bases (sodium alkoxides, sodium hexamethylsilamide) did not yield good results, and metal hydrides remained the choice of base for the reaction. With the concern of handling sodium hydride (despite the suspension in mineral oil) on large scale, we decided to use lithium hydride (LiH) instead. Lithium hydride presented several advantages. Commercial LiH granules are of good stability under storage (*33*). When milled LiH powder (0.28 µm size) is exposed to ambient air, the decomposition (forming a crust of Li_2O or LiOH) is an hour long process (*34*, *35*). It does not react with tertiary alcohols at room temperature (*36*, *37*).

These physical and chemical properties offer operational advantages in handling LiH in laboratory and production settings. Nevertheless, LiH is considerably under explored in organic chemistry due to the need of activation (for example, by treating with catalytic amount of Zn/TMSCl (*38*)).

After a brief screening, we quickly identified that the reaction to prepare **17** could be carried out with LiH in toluene with catalytic amount of ethanol for activation. To avoid any delayed reaction onset and achieve the best *cis/trans* selectivity, the reaction was empirically determined best to be carried out at 100 °C from the screening studies. Under such batch reaction conditions, the *cis/trans* selectivity was obtained in 9.8/1 ratio. The generation of hydrogen gas was a huge safety concern under batch conditions. In addition, the batch size would be severely limited by vent-size capacity of a reactor. With these in mind, we set forth to address the scalability by carrying the reaction under flow conditions.

Thermal stability analysis of the materials by DSC indicated that the 1% LiH solution in toluene was quite stable with a minor exotherm (ΔH -13.5 J/g) starting at about 186 °C. Thermal screening in an HEL Thermal Screening Unit also revealed that there was no risk of thermal decomposition generating non-condensable gas from an extended hold at 125 °C or when the sample was heated up to 200 °C. Neat ethyl acrylate had a very energetic exothermic (ΔH -830 J/g) decomposition starting at around 161 °C, but when this was combined with the other reactants and solvent (ethyl chloroaceate and ethanol), the thermal potential (ΔH -289 J/g) was reduced because of the dilution and the onset temperature (184 °C) was elevated.

2.1. Adapting the Batch Chemistry to Continuous Flow

When most chemists think of operating a reaction continuously, invariably, a system of pumps and chemically compatible tubing, such as PFA or PTFE is envisioned. Tubular or plug flow reactors are simple to assemble and many vendors provide standard kit units for exploratory chemistry development (*39*). If a slurry is encountered in development (either as a substrate feed stream or during the course of the reaction), thoughts of using a continuous reactor often turn back to optimization for batch conditions since slurries are difficult to model and predictions for larger scale reactions are not reliable. Another potential complicating factor for tubular reactor systems is in handling reaction mixtures in which a non-condensable gas is generated. At high temperature, a space where tubular reactors are highly leveraged, generation of non-condensable gases can create significant pressure demands potentially beyond the rated safety limits of the components of the system. Gas generation also impacts the desired control over the reaction residence time as pulses of gas and/or liquid can intermittently discharge out of the reactor outlet from the back pressure regulator.

The cyclopropanation reaction (Scheme 4) had both of these complicating factors in play. The LiH stream in toluene (one of the planned feed streams for the process) was a slurry and highly flammable hydrogen gas was generated as a byproduct of the reaction. Initial batch experiments were conducted at small scale to measure the reaction rate by FTIR (tracking the disappearance of ethyl chloroacetate by carbonyl stretch) and as a function of hydrogen gas generation by volume displacement. The bulk of the reaction appeared to be well-described by first order kinetics for both hydrogen gas evolution and from profiling the disappearance of the ethyl chloroacetate by IR (Figure 6). These experiments also indicated there was typically a short induction time prior to initiation of the reaction. This was associated with dissolution of the Li_2O protecting "film" around LiH with ethanol. A number of different data fits can be utilized to visualize the data and establish the order with respect to various species and the rate of the reaction (*40*). Alternatively, modern software packages such as Dynochem® may be used to perform the same task. Our analysis from following the disappearance of ethyl chloroacetate gave a first order reaction rate constant of approximately 0.09 min^{-1}. Other experiments provided reaction rate constants on the order of 0.046 min^{-1} to 0.06 min^{-1}, generally in line with initial observations.

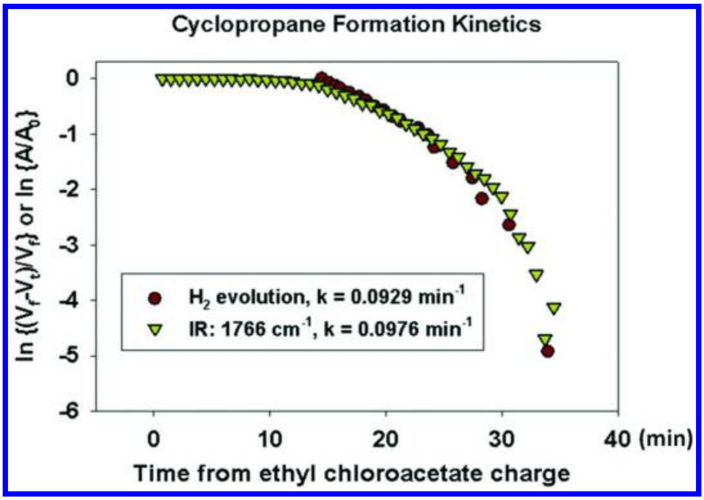


Figure 6. Batch reaction kinetics profiling.

Additional batch studies confirmed the presence of an induction period of a few minutes for initiation of the reaction. Once the reaction was initiated, it could be maintained by further addition of ethyl chloroacetate (studied up to the limits of stoichiometry). In some cases, the IR data gave a slightly better fit with zero order reaction than a first order process with respect to ethyl chloroacetate, indicating the complex nature of the reaction mechanism. For this particular reaction, additional ethyl chloroacetate was added in portions and the reaction rate was profiled (Table 1 and Figure 7).

Table 1. Comparisons of R^2 for Zero and First Order (*41*)

Charge	*Zero Order*	*First Order*
#1	0.975	0.915
#2	0.997	0.833
#3	0.985	0.858

In a second test, all of the reactants (ethyl chloroacetate, ethyl acrylate, ethanol and LiH in toluene) were added together into the hot reactor from the test above and in contrast with the first test above, the second test profile appears first order, but the signal is quite weak. The reaction was noted to proceed immediately with no induction period (Figure 8). This is attributed to initial activation of the LiH which was not necessary for the subsequent addition of the reactants into the hot reactor.

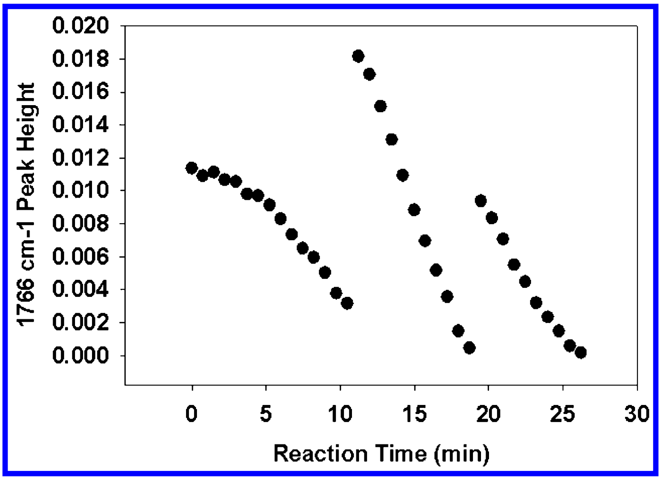


Figure 7. Reaction profiles with sequential ethyl chloroacetate charges

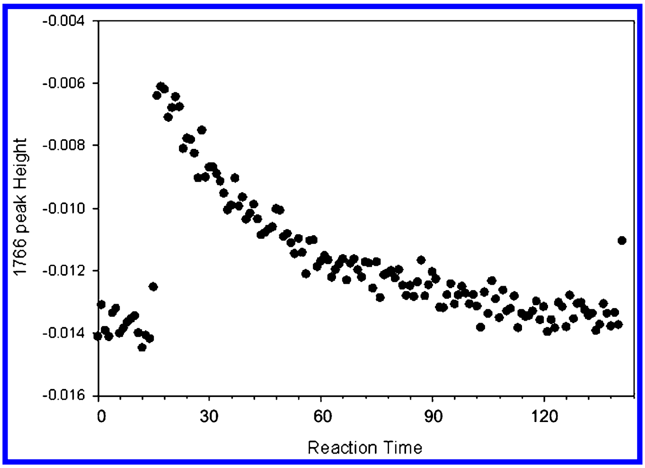


Figure 8. Reaction profile for addition of combined reactants to a hot reactor (added at 17 min)

In order to address the gas generation and slurry handling issues mentioned previously, a continuous stirred tank reactor (CSTR) system was envisioned. A CSTR looks very much like a batch reactor but feed streams are continuously added into the reactor while a discharge or product stream is continuously withdrawn. The input and output flow rates, the number of reactors, and the reactor volumes are selected to provide the desired reaction time (or residence time) the materials spend in the reactor. Once the reaction kinetics were established for our cyclopropanation reaction, CSTR reactor design equations were then used to determine the required reactor sizes necessary to achieve a desired conversion. We already had stirred reactor equipment of defined size and were planning on using two equally sized reactors for the primary reaction, so the design calculations were simplified to the following equation derived (*40*).

$$\tau_{\text{N reactors}} = \tau_i = [(1/(1\text{-X}))^{(1/\text{N})\text{-}1}\text{-}1]/\text{k}$$

The residence time, τ, for N reactors of equal volume is equal to the relationship shown above between the desired fractional conversion, X, and k, the reaction rate constant, which was established in the batch reaction experiments.

Our CSTR system consisted of two main reactors operating at about 800 mL volume followed by two smaller reactors operating at about 100 mL volume. These were fed into a larger 8 L reactor containing citric acid solution for the quench. For the case of 2 equal volume reactors (800 mL for our set up), a conversion of 88% would require a residence time of approximately 31 min using a value of 0.06 min^{-1} for the rate constant, derived from a batch reaction profile for formation of the cis product. The final smaller reactor was used to provide cooling to near ambient temperature for feeding the reaction mixture stream into the quench vessel.

Once we had our reaction kinetics developed from batch reactions and the design equation and set up in hand for the CSTR system, a safety assessment could be conducted prior to performing a test run in the CSTR system. The LiH slurry stream in toluene was generally well behaved in the flow system, causing some intermittent plugging issues at lower flow rates in the small diameter tubing. The input streams were pre-heated to provide better temperature control in the first CSTR, especially at startup. A nitrogen purge was provided at no less than 0.1 L/min through the system. This purge was set to approximately match the expected rate of hydrogen gas evolution at the planned reaction scale and ensure there was no build-up of flammable gas in the reactor system.

A potentially significant operational consideration for continuous flow systems is how to handle the startup and shutdown of the system. Flow systems require time to achieve a steady state which is the point at which a consistent, reproducible quality stream discharges from the system until a parameter change is made (feed rate, temperature, etc.). Generally, this time to steady state is related to the flow rates of the feeds and the volume of the system, but geometry and characteristics of mixing also play a role. For most systems, the output stream can be diverted to a separate collection vessel/area or wasted depending upon the specifics of the process and the actual condition of the stream. In the case of a CSTR specifically, there may be a significant delay from the start of the feeds until the desired volume in each reactor is achieved so that the discharge stream flow can then be initiated. This material may have spent a significantly longer period of time at the reaction conditions in each vessel as it is filling and may have a very different purity profile.

In our system, we pre-charged the reactors with some volume of solvent (toluene) to allow for stirring and heat-up of the contents in each of the reactors. The benefit of this is that when the feeds are initiated, the materials enter with the system already at the desired reaction conditions, avoiding any impact on not having agitation until suitable volume is achieved or having the mixture delayed in heating to the desired reaction temperature. The knock-on effect of operating at startup this way however, is that the initial streams are significantly diluted with excess solvent and it takes some time to come to the steady state concentration in each reactor vessel. For our particular cyclopropanation reaction, this did not have a significant effect on the reaction profiles or output quality. Each operating methodology must take into account the chemistry and behavior of the materials under study.

In a similar fashion, a protocol must be established for when the feed material is depleted or the system must be stopped for other reasons. In tubular systems, typically the feed would be switched over to a clean solvent to "push" the reaction materials through the system at the same flow rate to ensure similar residence time is achieved until the solvent starts to discharge. For the CSTR system, operating this way will further dilute the contents of each reactor in the system similar to the startup scenario above. At some point when flow is completely turned off, there will still be the holdup volume in the reactor that must be accounted for. In a simple case, these could simply be treated as batch reactors from that point and stirred at temperature to finish the reaction to the desired conversion before transferring out the contents. Alternatively, this material may have to be wasted in which case the system design may favor a larger number of smaller reactor vessels to reduce this loss of material.

2.2. CSTR Reaction Procedure

Quench Tank

Citric acid (300 g) in 3 L of water is under agitation in an 8 liter stirred vessel.

Stream A

Ethyl acrylate (450 g), ethyl chloroacetate (276 g) and ethanol (0.7 g) are combined under N_2 atmosphere.

Stream B

LiH (21.48 g) is suspended in anhydrous toluene (5.28 L) under N2.

Reaction Start up at T = 0 min

400 mL of toluene is charged to reactor vessel #2, and 100 mL of toluene each to reactor vessel #3 and #4. Outlet of reactor vessel #4 is run via peristaltic pump to the quench tank. Each reactor vessel is equipped with a reflux condenser. Maintain nitrogen purge through system at no less than 0.1 L/min. The vessel train is heated to 100 – 105 °C, and inlet heat exchanger to 85 °C.

Starting the Reaction

Start stream B pump at 17.4 mL/min and stream A pump at 2.63 mL/min (Pumps are calibrated with actual feeds prior to beginning reaction). When reactor vessel #4 reaches overflow, start outlet pump. Both pumps are shut off when one feed stream is depleted. A 300 g run over approximately 7 hours was demonstrated using a CSTR rig as shown in Figure 9 and Figure 10. 88% conversion was observed, consistent with predicted from kinetics modeling.

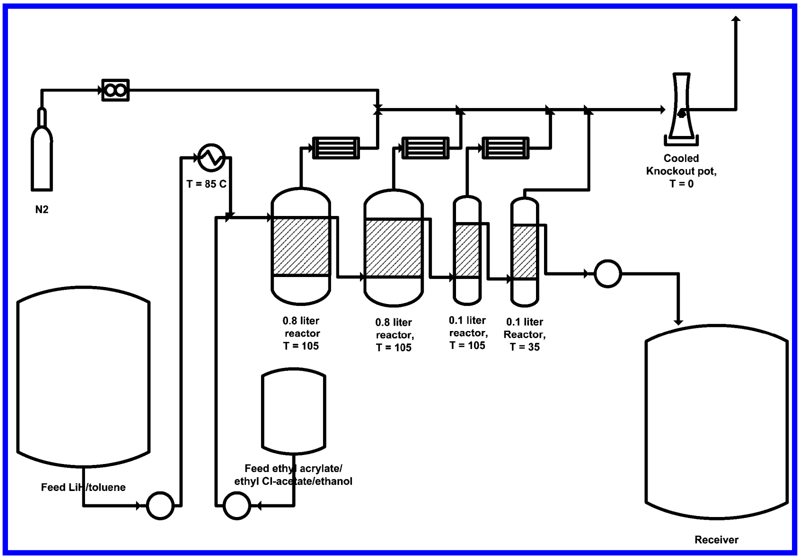


Figure 9. CSTR rig with a train of 2 x 800 mL and 2 x 100 mL reactor vessels.

Workup and Isolation

The quench tank contents are allowed to settle in 1 - 2 h. The phases are split, and the organic phase is washed with saturated sodium bicarbonate solution and brine solution successively. The organic phase is then concentrated to give a mixture of crude products as an oil (8.4 *cis/trans* ratio, only slightly lower than conditions obtained in small scale batch reactions to establish kinetics). The crude material is passed through silica gel pad (100 wt% of the crude) and eluted off with 4:1 heptanes/EtOAc (10 mL/g). The product-rich fractions are combined and concentrated to a light yellow oil. This is further purified by high vacuum distillation (125 - 126°C, 12 Torr) to give diethyl cyclopropane-*cis*-1,2-dicarboxylate as a colorless oil (42% yield from a 300 g run).

Figure 10. Photo of CSTR rig set up with a train of 2 x 800 mL and 2 x 100 mL reactor vessels.

2.3. Summary

We have described a flow process allowing the safe handling of a slurry reaction with generation of highly flammable hydrogen gas in a CSTR system. Batch reaction kinetics were established and used to design the CSTR, providing an observed conversion of 88% as predicted from the design equation for the two equally sized reactors. The solid/liquid heterogeneous reaction mixture using lithium hydride was successfully handled at multi-gram laboratory production scale (2x800 mL CSTRs, producing ~300 g of cis cyclopropane 17 after about 7 h of operation). Process robustness at larger scales and for longer durations was not tested; however, the knowledge gained from the laboratory CSTR flow design will prove invaluable for other heterogeneous solid/liquid reactions with concurrent flammable gas generation.

3. Conclusion

Despite a great number of examples of continuous processes reported in the literature, the technology remains considerably underutilized in the pharmaceutical industry. In particular, when solids are present in reaction streams, the adoption of flow processes becomes more challenging, therefore requires more engineering and developmental efforts. In this chapter, we have presented two examples that involved the handling of solids. In the first example, while the feed streams were homogeneous solutions, the intermediate (diazonium salt) precipitated out of the reaction stream. The characteristics of solids (light and loose), coupled with the use of FMI pumps (some pulsating effect), allowed the solids move smoothly. In the second example, LiH, as a heavy solid powder, was present in a feed stream, the feeding was handled with a precalibrated peristaltic pump and the reaction was carried out in a CSTR system that effectively managed both the LiH powder and hydrogenation evolution of the reaction.

With the complexity of chemical processes in the pharmaceutical industry, it is imperative that process chemists and chemical engineers work closely as a team to implement the flow technology. The design of a continuous process reactor should include reactor type, pumping mechanism, reactor dimension and mixer type based on the understanding of chemical and physical characteristics of process streams, heat and mass transfer, and reaction kinetics.

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28. Demethylation using BCl_3 was not clean probably due to the methyl chloride formed was trapped under the reaction conditions. See also Li, B.; Samp, L.; Sagal, J.; Hayward, C. M.; Yang, C. *J. Org. Chem.* **2013**, *78*, 1273–1277.
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Chapter 15

Technology for Continuous Production of Fine Chemicals

A Case Study for Low Temperature Lithiation Reactions

L. Mleczko[1],* and Dongbo Zhao[2]

[1]Bayer Technology Services GmbH, 51368 Leverkusen, Germany
[2]Bayer Technology and Engineering Shanghai Co., Ltd., 201507, P.R. China
***E-mail: leslaw.mleczko@bayer.com)**

This chapter introduces the concepts of flow technology primarily in relationship to the use of organolithium reagents and reactions, and describe a workflow for flow chemistry and micro-reaction technology along with the necessary infrastructure with suitable equipment at different scales for the lithiation of chloroarenes. This work highlights the many advantages of flow chemistry in transferring a potentially hazardous laboratory scale reaction into a viable large scale operation. In all aspects, continuous lithiation of fluoroaromatics was superior to the corresponding batch processes.

Introduction

For decades, production technology for the fine and pharmaceutical chemicals has been based on batch-operated stirred-tank reactors. This approach is well founded since it is a very flexible and robust technology. It is product and reaction independent as batch reactors can be easily adapted to different reaction rates by changing the batch time or the temperature. By using enameled or glass-lined reactors even very corrosive liquids can be processed nor is pressure an issue for appropriately engineered reactors. Slurries can be easily processed and there is extensive knowledge available as to how to design a stirrer as well as what other measures can be used in order to improve mixing efficiency.

In Managing Hazardous Reactions and Compounds in Process Chemistry; Pesti, et al.;

Highly exothermic reactions can be managed safely by semi-batch operation, i.e. by controlled feeding or dosing of one of the reactants. If this measure is not sufficient to dissipate the evolved reaction heat, then a heat exchanger in various configurations can be employed as well. However, there is still room for improvement in designing equipment to react chemicals.

Scale up in batch reactors is simple since it is only influenced by the quality of mixing and the ability of the reactor to remove heat. Generally scale-up is realized by performing the reaction in increasingly larger vessels. No wonder that for many years, fine chemical technology was largely reserved for chemists who directly adapted their laboratory processes into the plant. For chemical engineers it was the technological desert. This situation even impacted the curricula at universities (*1*). However, the last two decades have produced some novel trends in reactor technology more focused toward engineering. Two technologies have come in fashion: "micro reaction technology" (MRT, (*2–7*)) and "flow chemistry" (FC, (*8–17*)). MRT has its roots in the mid-1990s and its use is dominated by chemical engineers. FC is younger and is dominated by chemists.

MRT originated as a spin-off of the general technological trend of miniaturization, mainly driven by the electronic industry and was enabled by new manufacturing technologies. This example of "technology push" brought for researchers and industry a novel set of devices called micro-mixers, micro-reactors or micro-heat exchangers. This new category of equipment utilized micrometer-sized channels for performing operations such as mixing, reaction and/or heat exchange. The excellent radial mixing in these narrow channels, that are comparable with the diffusion parameters, produced a very narrow residence-time distribution such as found in plug-flow systems. This in turn promoted a high selectivity [defined as the % of desired reaction versus all reactions that occur in this step] in complex reaction networks, including polymerization or nanoparticle synthesis in flow to give narrow molecular weight distribution or particle size distribution, respectively. The large surface-to-volume ratio allows extremely efficient heat removal. This feature is important to prevent run-away reactions and achieve isothermal operation, even for highly exothermic reactions that could not be accomplished using batch conditions. Finally, MRT promised easy scale-up by numbering up the cheap machine-made modules.

The flow-chemistry approach is to use millimeter-sized capillaries as a continuous reactor. Flow-chemistry has its roots in recognition that when performing a reaction in a capillary, it is easier to remove heat as compared to a flask, due to the superior surface to volume ratio of small equipment. This provides an avenue to speed-up reactions by operating at higher temperatures while still maintaining safe operation.

Following these trends, a number of reaction classes have been studied over the last two decades applying continuous flow, either using micro-reactors or in capillaries (*18*). An entirely new scientific community has emerged described in symposia series, journals (*8–17*) and textbooks (*2–7*). On the other hand, transfer of scientific achievements into industrial practice has faced a number of barriers and the earlier expectations have yet to be fulfilled. In spite of the remarkable potential of MRT, examples of transferring the technology from the laboratory into industrial applications have remained infrequent.

One of the primary barriers that have prevented effective transfer from laboratory to large scale production is the selection of suitable reaction systems that may benefit from operating in continuous mode. In 2005 Roberge et al. (*19*) performed a thorough analysis of the potential of MRT for the fine chemical industry. His analysis was based on classifying synthetic processes according to their relative speeds of reaction, mixing, and heat transfer. He concluded that the main motivation to use MRT in large scale operations would be improving reaction yields and/or safety. Additionally, the gain in reaction yield resulting from using MRT must be sufficiently significant to compensate for the increased investment in time, capital and resources. Roberge estimated that ca. 50% of the reactions in the fine chemical and pharmaceutical industry could benefit from use of a continuous process based mainly on micro-reactor technology.

A similar assessment was performed by Bayer Technology Services (BTS) (*20*) in which reactions studied using MRT were evaluated and compared to classical processes using reaction yields and product qualities as criteria. It was estimated that about 27% of the studied reactions performed better under MRT conditions than in conventional processes while about 10% of the studied examples performed worse. This does not necessarily mean that the remaining 63% of reactions could not have benefitted from MRT. Indeed many of them would improve simply due to the reduction in safety hazards. Nevertheless, only 8% of the investigated cases managed to reach pilot-scale. Therefore, clear selection criteria are necessary for pre-assessment of which reaction systems are suitable for MRT to avoid wasting resources. Analysis of the speed of reactions derived from the fine chemical and pharmaceutical industries (*19*, *21*, *23*) identified three classes of reactions:

- Type A reactions are very fast with a reaction half-life of less than 1 s. Such reactions take place mainly in the mixing zone and are controlled by the mixing process (micromixing domain). The flow rate and the mixer type play an important role. To this category fall organometallic reactions, e.g. lithium and Grignard type chemistry. These reactions usually require cryogenic temperatures.
- Type B reactions are rapid reactions, with reaction times between 1 s and 10 min. They are controlled not by mixing but predominantly by the kinetics. These reactions would benefit from a microstructure in order to control reaction temperature. However, these reactions could also be performed in conventional equipment but lower yields would result due to the difficulty of temperature control.
- Type C reactions are slow (> 10 min) and they can usually be performed in classical equipment. However, a continuous process could still derive advantages in regards to safety or product quality.

Roberge found that 44% of reactions performed at Lonza belonged to groups A & B. However, when solids-free systems were considered which are needed for microreactors, only 17% of these reactions qualified.

Another reason for the slow industrial scale deployment of continuous chemistry technology is the lack of suitable hardware. Equipment utilized for research is usually of limited capacity, i.e. the typical throughput is in the range of millilitre per minutes. Although at laboratory-scale, micro-mixers can manage exothermic reactions since heat removal is facile, it would require a re-design of the corresponding reactor and heat exchanger for the up-scaled process. Additionally, the flexibility in capacity and residence times for MRT systems is rather different from that of conventional batch systems, which have been elaborately investigated with other examples available to quickly adapt and compete in the dynamic fine chemicals marketplace. The originally proposed scale-up approach of MRT systems by simply numbering up simply became too expensive. And simple solutions, such as the use of capillaries, are not scalable at all. Finally, scale-up efforts became much more complex when compared to batch stirred tanks. The competence fields that had to be addressed when developing a FC based technology are similar to that when developing a batch process for large-scale bulk chemicals (*22*). Since not only the reaction but also the entire process along with associated infrastructure had to be scaled-up, MRT based processes are no longer micro or portable in nature.

In order to overcome these obstacles and exploit the potential utility of flow chemistry and micro-reaction technology, it is important to demonstrate multiple successful larger scale examples to establish the robustness of this approach. Such successful examples will facilitate the acceptance of MRT as a reliable and recognized technology. The increased utilization of the technology will in turn demonstrate its maturity and will establish the rules for its development and industrialization. In this chapter we review the present state of continuous processing related to the chemistry we wish to establish and present an example that demonstrates the development activities to take a batch reaction and scale it up to a continuous process. The strategy aimed at application of flow chemistry for fine chemicals production is based on following steps:

- Selection of the proper reaction system – it should belong to either group A or B
- Selection of scalable hardware for performing the required chemical transformations
- Two stage technology development – laboratory followed by the pilot scale
- Design and engineering of a skid mounted unit that includes both the unit operations part as well as the required instrumentation for autonomous operation.

The BTS strategy that forms the development platform for the MRT-based processes is illustrated in Figure 1. Low temperature arylmetallation of fluoroaromatics [organolithium chemistry] has been selected for the model reaction system.

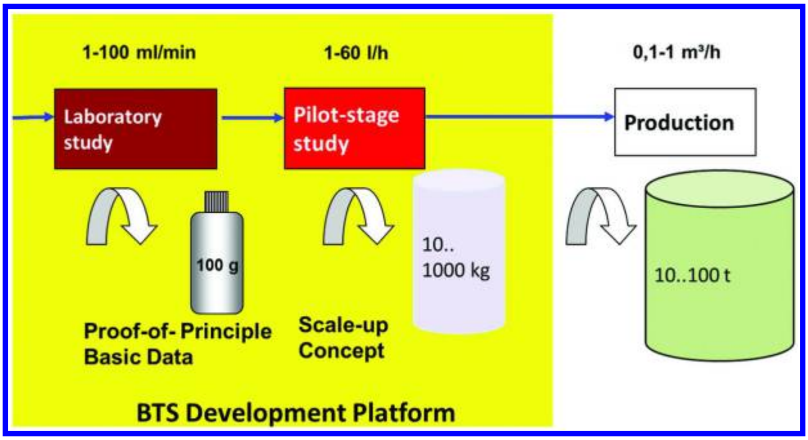


Figure 1. Development concept for MRT-based processes

Discussion and Results

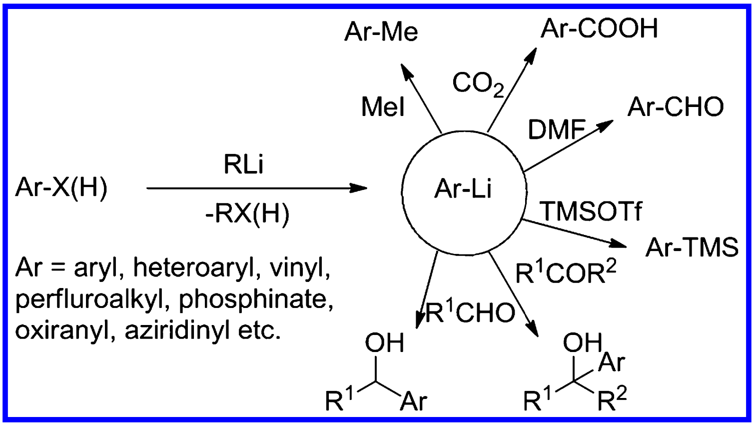
Organolithium Chemistry in Flow

Lithium Chemistry in FC and MRT

Organolithium compounds serve as useful carbanion equivalents in chemical synthesis (*7*, *24*). Since organolithium reactions are often extremely fast and highly exothermic as well as producing unstable compounds, they are usually performed at low temperatures to maintain their integrity. Due to the high reactivity of organolithium compounds, usually a semi-batch operation with slow addition of one of the reactants to control heat generation is used. Batch or semi-batch operation often has implications for the selectivity and integrity of the reaction due to the instability of many organolithium compounds. Organolithium reactions are also challenging with respect to safety, both for the reactivity of these strong bases and occasionally explosive behavior. This requires special measures to prevent run-away reactions that could lead to disaster.

When considering these features of organolithium reactions and comparing them to the criteria described above, it is clear that they are well suited candidates for FC and MRT applications. Usually organolithium reactions are classified as Type A (instantaneous, mixing controlled) or Type B (rapid, kinetically controlled). An important value of MRT operation is that it is well suited for in-situ generation of unstable intermediates. Highly efficient mass and heat transfer in MRT enables a significant reduction in residence time. The short residence time inherent fo0r flow micro-reactors is useful for controlling reactions involving unstable, short-lived reactive intermediates. Unstable reactive species can be generated in situ and reacted before they decompose. By taking advantage of this feature, chemical transformations that are very difficult or impossible to operate in “macro-reactors” can be achieved in micro-reactors.

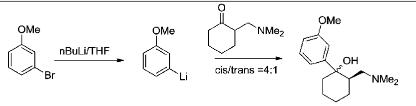
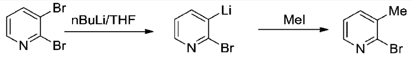
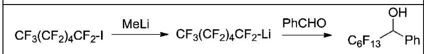
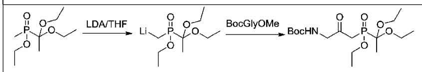
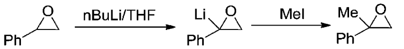
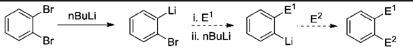
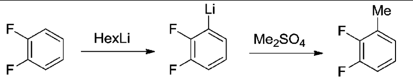
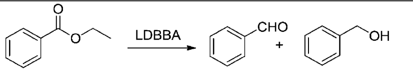
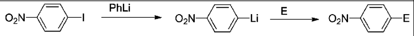
One of the classic applications of organolithium reagents is lithium-halogen exchange or de-protonation of substrates followed by reaction with an electrophile (Scheme 1). In general, many common electrophiles may be reacted with organolithio intermediates including: aryl halides (*25*), heteroaryl halides (*26–28*), vinyl halides (*29*), perfluoroalkyl halides (*30*, *31*), phosphinates (*32*), epoxides (*33*) and aziridines (*34*). For example electrophiles such as iodomethane (*35*), methanol (*36*), chlorotrimethylsilane (*35*), chlorotributylstannane (*35*, *36*), methyl triflate (*36*), trimethylsilyl triflate (*36*), chlorotributylstannane (*36*), aldehydes (*35*, *36*), ketones (*25*, *26*, *35*, *36*), dimethyl sulfate (DMS) (*37*), dimethylformamide (DMF, (*38*), borate (*39–42*) and carbon dioxide (*43*, *44*) have been utilized in flow chemistry syntheses. In addition, reduction reactions with $LiBH_4$, $LiAlH_4$ or their modified forms may be optimized by using flow chemistry to give better selectivity and/or higher chemical yields (*45*, *46*).



Scheme 1. Lithium-halogen exchange or de-protonation followed by the reaction with selected electrophiles.

Table 1 summarizes the results from several successful examples that demonstrate the transfer of organolithium reactions from batch to continuous reactions by means of FC. These examples illustrate that by application of FC, higher yields or less byproducts, significantly reduced residence time, and avoidance of cryogenic conditions have been achieved compared with conventional batch processes. There are already many reports of successful flow lithiation (*25–46*) and a monograph (*7*) on the advantages of flow processes over their batch counterparts. Thus our review will cover only recent progress on the use of FC for sensitive or configurationally unstable intermediates, non-protecting group synthesis, selectivity-controlling/switching reactions as well as integrated multi-lithiation/step reactions.

Table 1. Comparison between batch and continuous flow processes*

Reaction Scheme	*Temp. (°C)*		*Time (s, min, h)*		*Yield (%)*		*Ref.*
	batch	*Conti.*	*batch*	*Conti.*	*batch*	*Conti.*	
	-65	-14	n.a.	17 s	80	87	25
	-78 (-28)	0	10 min	0.06 s	48 (0)	87	27
	-78 (0)	0	1 min	2.09 s	67 (46)	80	31
	-78	35	1h/45 min after slow addition	1.5-2 min	n.a.	24-26	32
	-95 (-78)	-78 (-48)	1 min	23.8 (1) s	n.a. (34)	88 (60)	33
	-110 (-78)	-70	Slow addition	0.82 s	n.a. dcmp	70	36
	-78	-40	Slow addition	<5 min	89	94	37
	0	0	180 min	10-20 min	74	79	46
	impossible	-28	-	0.01 s	0	86	59

*Note: The numbers in parentheses mean other conditions and the corresponding results for either batch or continuous processes.

Easily Decomposed or Configurationally Unstable Intermediates

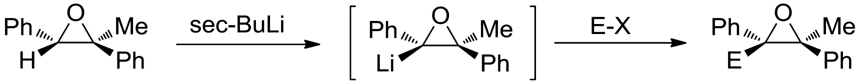
The use of microreactors and flow chemistry for unstable intermediates is typically superior to batch reactions. It has made it possible to carry out many transformations efficiently and under significantly milder conditions with equivalent or better results. The following examples illustrate some useful applications:

a) The Yoshida group (*36*) investigated the Br–Li exchange of *o*-dibromobenzene followed by the reaction with an electrophile at −78 °C using a flow micro-reactor. It should be noted that this reaction would be carried out at −110 °C or below in a batch stirred-tank reactor because the elimination of LiBr to form benzyne is very fast even at −78 °C (*47*). Regarding the instability of many organolithium intermediates, temperature control, sometimes combined with residence time control, is crucial in order to avoid decomposition at the critical reaction temperature.

b) Perfluoroalkyllithiums are often prepared by halogen–lithium exchange of perfluoroalkyl halides with alkyllithiums, but they will readily undergo β-elimination to form perfluoroalkenes (*48*). Flow micro-reactors provide an efficient method for preparing perfluoroalkyllithium intermediates (*31*). There are two methods: the normal stepwise process of perfluoroalkyllithium generation followed by trapping with an electrophile in a separate step, or generation of perfluoroalkyllithium and in situ trapping with an electrophile. The second procedure is a better method since it often circumvents the problem of β-elimination via rapid consumption of the organolithium intermediate. Flow micro-reactors are more advantageous for both procedures. In the former method, β-elimination of LiF was avoided by virtue of a short residence time and efficient temperature control as compared to batch reactions. In the second procedure, the reactions can be conducted at much higher temperatures than those required for batch stirred-tank reactors. However, only the former stepwise method was effective with highly reactive electrophiles such as chlorotributylstannane, trimethylsilyl triflate, and isocyanates, which are not compatible with the lithiation process.

c) Flow micro-reactors enable the rapid generation of configurationally unstable organolithiums and the subsequent reaction with an electrophile before they epimerize. For example, the short residence time in a flow microreactor allowed the in-situ formation of the configurationally unstable α-aryloxiranyllithiums by the deprotonation of a series of di- or tri-substituted epoxides in the presence of electrophiles (*49–52*). As shown in Scheme 2, the unstable intermediate immediately reacted with the electrophile without isomerization or decomposition, achieving the diastereoselective synthesis of tetrasubstituted epoxides by using an integrated flow microreactor (*33*).

d) Configurationally unstable enantioenriched chiral organolithiums were generated (Figure 2) by enantioselective carbolithiation of conjugated enynes in a flow micro-reactor (*53*). Subsequent reaction with electrophiles would produce enantioenriched chiral allenes by residence time control to avoid any epimerization.



Scheme 2. Diastereoselective flow synthesis of tetrasubstituted epoxides via the configurationally unstable α-aryloxiranyllithium intermediate

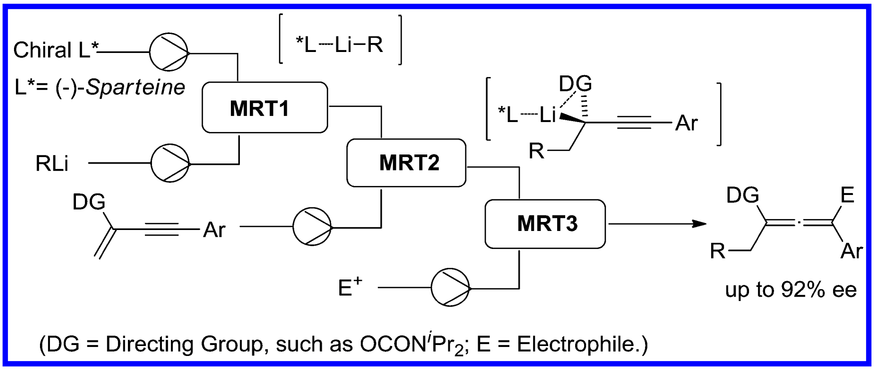
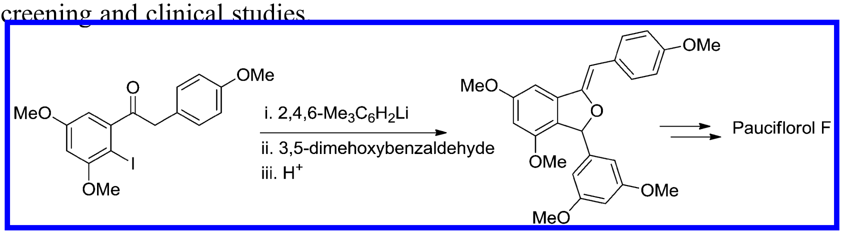


Figure 2. Flow synthesis of enantioenriched chiral allenes by carbolithiation followed by trapping with electrophiles

Non-Protecting Group Synthesis

The concept of the protecting group (*54*) is important in organic synthesis. For instance, functional groups, such as ketones, esters and nitro groups are not inert to organolithium reagents and thus need to be protected when subjected to the lithiation process then de-protected afterwards. However, recently an exceptional alternative process has been developed using a flow microreactor that enabled a protecting-group-free organolithium reaction by reducing the residence time to $t \leq 0.003$ s (*55*). Aryllithium species bearing unprotected reactive functional groups such as ester, nitro, cyanide or ketone carbonyl groups were directly generated in flow reactors by Li-halogen exchange of the corresponding aryl halides with organolithium reagents and then reacted with various electrophiles. As the kinetics of the electrophilic capture of the organolithium intermediate was much faster than any reaction with the vulnerable moieties at the higher temperatures used (as compared to batch reactions), the reaction was viable. In most cases, this reaction is impossible for batch operation even at very low temperatures.

An example of a practical application of this effective methodology is the formal synthesis of pauciflorol F (*55*). A key intermediate in the synthesis was prepared via the lithiation of an aryl iodide containing an unprotected ketone group with 2,4,6-$Me_3C_6H_2Li$ in a flow microreactor (Scheme 3). Notably, the productivity is relatively high (1.06 g over 5 min) and provides an efficient way of producing this useful pharmaceutical compound in sufficient amounts for screening and clinical studies.



Scheme 3. Key steps in the flow synthesis of pauciflorol F

Selectivity Controlling/Switching Reactions

Due to the high reactivity of organolithium reagents, the selectivity issue is another important concern. Accordingly, selective Li-halogen exchange and subsequent reactions depending on the basis of either the kinetically formed organolithium species or the thermodynamically preferred isomer, have been studied. For instance, consider the selective initial lithiation of polysubstituted halogenated aromatics followed by trapping with an electrophile; subsequently followed by further lithiation of another halogen and a different electrophile, to generate unsymmetrically substituted biaryls. The monolithiation of *m*- and *p*-dibromobenzene (*35*) at 0.39 s residence time at 20 °C in flow versus −48 °C in batch and *o*-dibromobenzene (*36*) at 0.82 s residence time at -78 °C in flow versus -110 °C in batch with *n*-BuLi followed by the reaction with an electrophile could be realized using a flow microreactor.

Furthermore, the reaction pathways of organolithiums can be manipulated at times by targeting either the kinetically formed organolithium species or the thermodynamically preferred isomer, contingent on the residence time and temperature control allowed in a flow microreactor. As shown in Figure 3, the residence time control was essential to the selective formation of either the kinetically formed arylithium (shorter residence time of 0.06 s at −48 °C) or the thermodynamically stable arylithium species (longer residence time of 62 s) after the Br–Li exchange of 1-bromo-2,5-dimethoxy-3-nitrobenzene, and the trapping with an aldehyde gave the corresponding products in 84% and 68% yields, respectively (*59*).

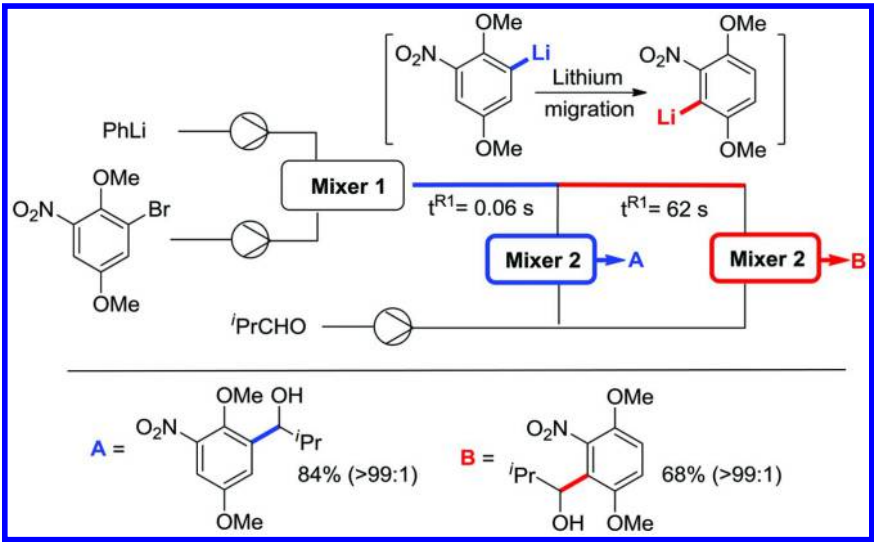


Figure 3. The selective formations of kinetically and thermodynamically stable aryllithium species by tuning the residence time in flow systems, followed by trapping with an aldehyde.

Applying the same strategy, the switching of the reaction pathway of heteroaryllithiums such as benzo[*b*]thiophen-3-yllithium and benzo[*b*]furan-3-yllithium was possible (*60*) and thus enabled the reaction with an electrophile before or after ring-opening (Figure 4). Additionally, the switching of the reaction pathway of 1,2-dichlorovinyllithium generated from *trans*-1,2-dichloroethene was successfully realized (*61*) yielding the corresponding alkenes and alkynes selectively (Scheme 4).

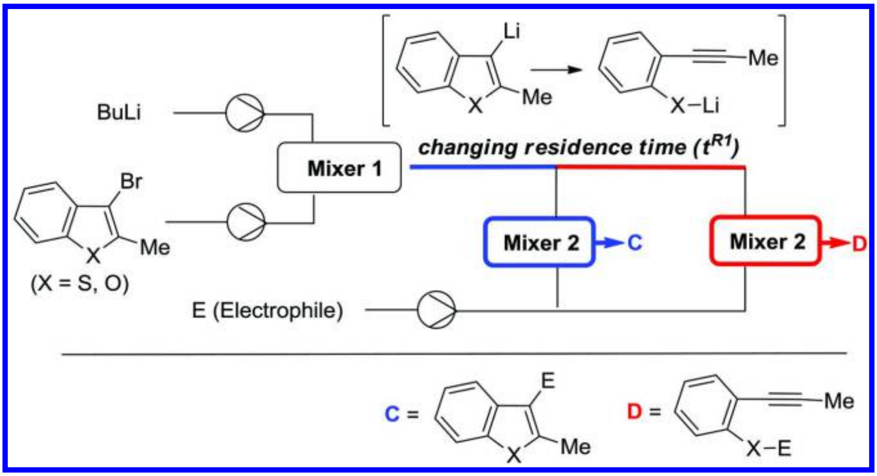
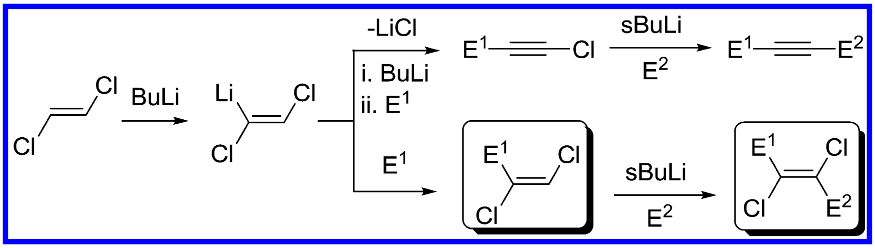


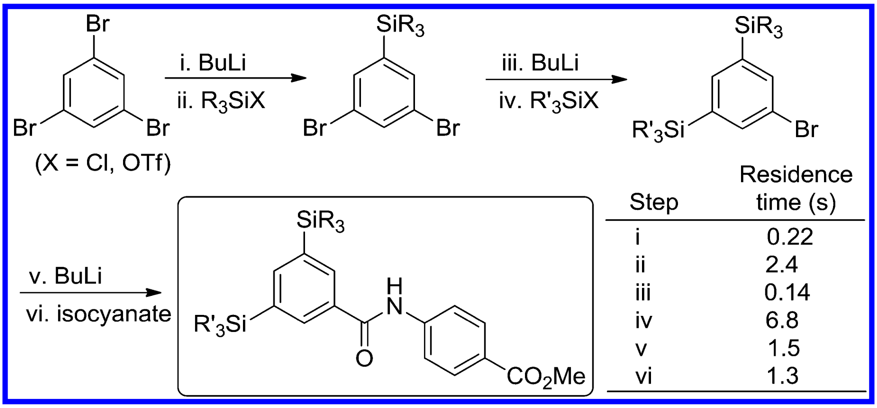
Figure 4. Reaction-pathway control before or after ring-opening by choosing an appropriate residence-time and temperature in flow microreactor systems.



Scheme 4. Versatile synthesis of alkenes and alkynes from trans-1,2-dichloroethene.

This methodology was further extended to selective monolithiation or dilithiation of dibromobiaryls (*56*, *57*) and dibromopyridines (*27*, *28*) to produce the corresponding mono- or di-substituted biaryls and pyridines, respectively. On the basis of those findings, the synthesis of TAC-101 (4-[3,5-bis(trimethylsilyl)benzamido]benzoic acid), a retinoid targeting human promyelocytic leukemia cells HL-60, was successfully achieved from 1,3,5-tribromobenzene, by integrating three sets of Br–Li exchange followed each time by reaction with an electrophile in one flow experiment without isolating the intermediates (*58*). As shown in Scheme 5, this multiple flow synthesis of

TAC-101 demonstrated the high efficiency and flexibility to produce various methyl ester analogs containing different silyl groups in good yields and high productivity (132 to 194 mg/min at 12.2 s of total residence time). A special micromixer-integrated microtube reactor was fabricated.



Step	Residence time (s)
i	0.22
ii	2.4
iii	0.14
iv	6.8
v	1.5
vi	1.3

Scheme 5. Flow synthesis of TAC-101 and its analogs.

$LiAlH_4$, $LiBH_4$ and/or their substituted and modified derivatives are strong and versatile reducing agents in conventional organic synthesis. But in batch processes, the selectivity control, sometimes balanced with productivity, would be problematic even at low temperature and slow additions. By using flow reactors, it is possible to achieve selective stoichiometric reduction of reducible functional groups. For example a flow protocol for stoichiometric reductions of artemisinin to dihydroartemisinin (DHA) in high yields using $LiBHEt_3$ at room temperature has been demonstrated (Figure 5). Short residence times and full conversion in high overall productivity ~1.60 kg h^{-1} L^{-1} was achieved for both α- and β-epimers (*45*). This represents a 42 fold increase in throughput compared to that of a conventional batch process.

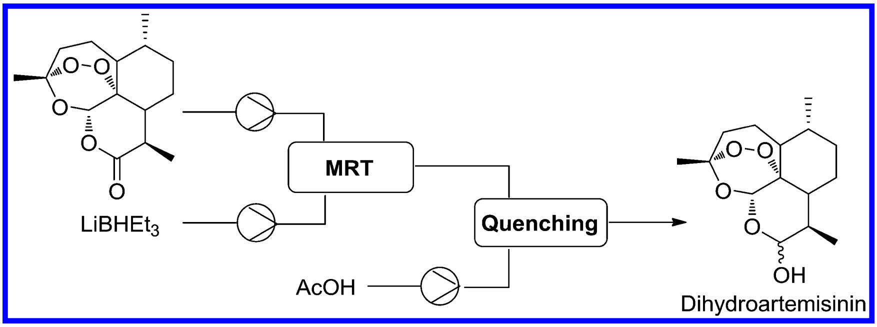


Figure 5. Flow reduction of artemisinin to dihydroartemisinin at room temperature.

Another example of flow chemistry as a viable alternative to batch procedures is the reduction of esters to aldehydes using lithium diisobutyl-*tert*-butoxyaluminum hydride (LDBBA) (*46*). This citation includes the selective reduction of a single ester group in a symmetric di-ester (Figure 6), which cannot be achieved under traditional batch conditions. It also includes the selective reduction of an ester group in the presence of an aldehyde and the selective reduction of a primary ester in the presence of a secondary ester.

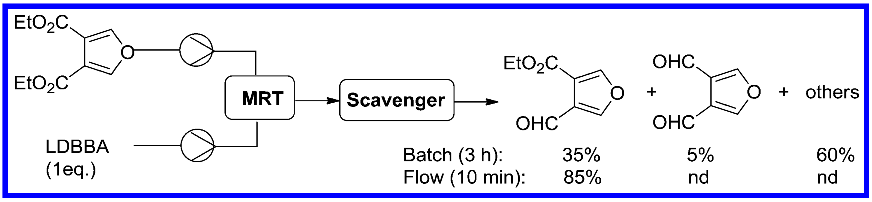


Figure 6. Selective reduction of a single ester group under flow conditions.

Integrated Multi-Lithiation/Step Reactions

One of the most attractive developments of organolithium chemistry in the field of flow microreactors is the use of sequential multistep transformations because they can result in less waste from fewer purification steps and less manipulations of intermediates. Compared to single step processes, the development of multistep continuous-flow syntheses remains a particularly difficult challenge due to the increased complexity from factors such as flow-rate synergy, solvent compatibility, and the effect of by-products and impurities. This concept is illustrated by continuous metal-catalyzed coupling reactions such as Pd-catalyzed Murahashi coupling with aryl halides that use aryllithiums generated from halogen-lithium exchange in microreactors (*62*). In this case, the major problem is the formation of the byproduct BuBr from the bromine–lithium exchange step. The presence of BuBr causes serious side reactions if the subsequent Murahashi coupling reaction is slow. However, the integration of multistep reactions in flow provides a very fast and effective method for the coupling of two different aryl and heteroaryl bromides to give the corresponding biaryls and biheteroaryls, using the optimized catalyst PEPPSI–SIPr. This methodology was further extended to coupling with vinyl halides and oxidative homocoupling (*63*, *64*).

In another example, a multistep flow lithiation/borylation/Suzuki–Miyaura cross-coupling process has been developed (*65*). In this process the handling of solids in the stream with the help of acoustic irradiation enabled easy operation at ambient conditions to produce a synthetically useful biaryl intermediate towards Diflunisal. A similar concept has been reported for the synthesis of biaryls via functionalized boronic esters, but mainly focusing on the cross-coupling of two aryl halides bearing electrophilic functional groups without added base (*66*).

Similar to the above-mentioned example in Ref. (*65*), efficient solids-handling with sonication was enabled for the flow synthesis of enantiopure β-arylated ketones by a lithiation/borylation/1,4-addition sequence (*67*) as the first example of a multistep asymmetric catalysis reaction in flow (Figure 7). Of importance is that this process uses readily available and inexpensive aryl bromides instead of arylboron reagents, operates at mild temperatures and obviates the need for isolation or purification of intermediates.

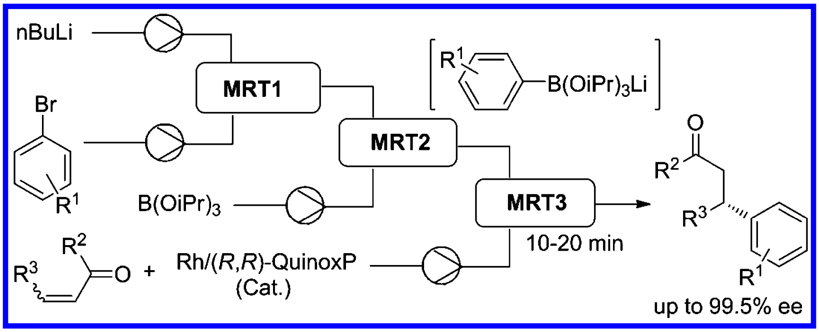


Figure 7. Flow synthesis of enantiopure β-arylated ketones by lithiation/borylation/1,4-addition sequence

As mentioned above, benzyne formation (*36*, *37*) is problematic for many reactions of *o*-haloaryl lithium intermediatess due to their instability. However, benzynes can be useful synthetically in organic synthesis and thus the preparation of their precursors is important. Michel et al. (*68*) reported a novel continuous flow process for the synthesis of 2-(trimethylsilyl)phenyl triflate and nonaflate aryne precursors in excellent yields with no requirement for low temperature lithiation. The productivity for this flow process could reach 20 mmol of product per hour by a multistep lithiation and retro-Brook rearrangement sequence (Figure 8). Another benefit to using flow was the utilization of cheaper and more user-friendly nonaflyl fluoride reagent instead of the toxic Tf_2O.

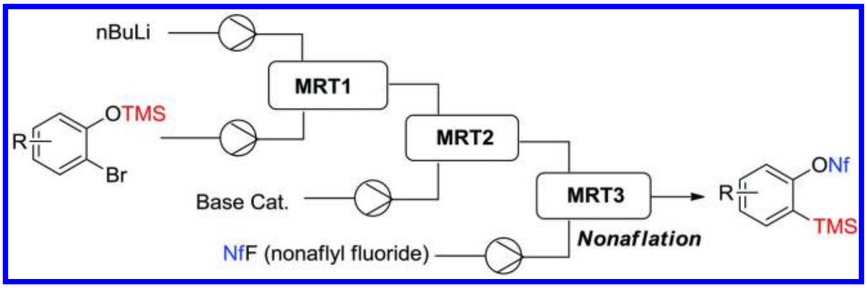


Figure 8. Flow synthesis of aryne precursor by a lithiation/retro-Brook rearrangement sequence.

The continuous flow protocol for the preparation of the tricyclic antidepressant amitriptyline by applying multiple organolithium generating reactions combined with carboxylation, the Parham cyclization and other key synthetic steps, has been developed (*69*) (Figure 9). More recently in 2014, Umezu et al. (*70*) reported the generation of ynolates via reductive lithiation using flow micro-reactors followed by the subsequent olefination of carbonyl compounds. Compared with the corresponding batch counterpart, which required low temperature control and extended reaction time up to 1 h, this multistep flow process could be completed at 0 - 25 °C within only one min.

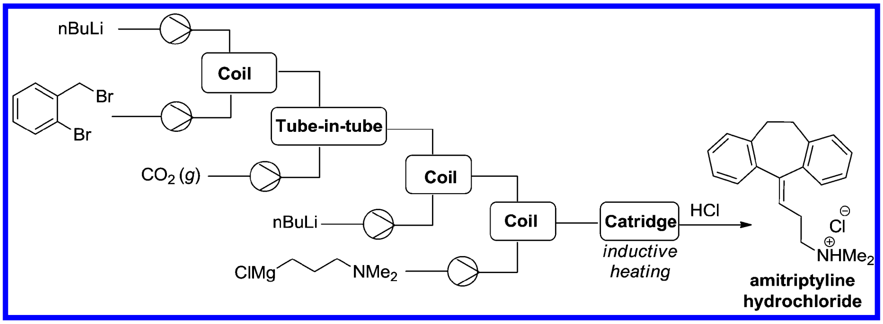


Figure 9. Continuous flow preparation of amitriptyline HCl.

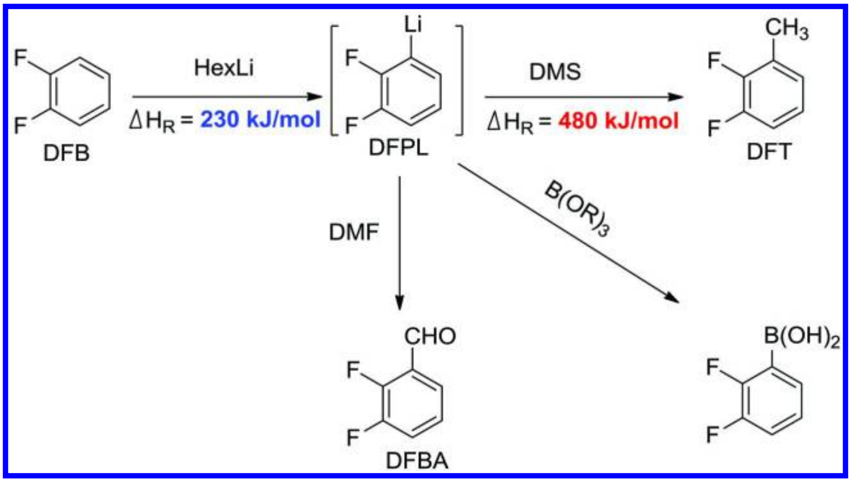
In summary, organolithium chemistry has been significantly improved in versatility after the integration of MRT or FC technology, demonstrating significant advantages over conventional batch processes. These improvements include easier operation due to higher reaction temperatures, better selectivity/ yield due to suppressed side reactions, and integration of batch and continuous processes or multistep flow processes. However, most flow applications for the synthesis of fine or pharmaceutical chemicals are still confined to lab scale in terms of capacity (Table 2). And there are only a few reports to date regarding prototype/ commercial cryo-reactors (*71–73*), (please also see the following section titled as “Scalable Modules for Flow Chemistry”) or pilot plants (*74*, *75*) for organolithium chemistry in flow microreactors. Clearly, this is an area for industry to exploit to enable large scale preparations of previously unattainable chemistry.

Reaction Selection

Based on the potential of MRT and FC for lithiation reactions, the 2,3-difluorotoluene (DFT) and difluorobenzaldehyde (DFBA) syntheses have been selected as model reactions. The goal of the study was to develop a MRT-based technology to enable commercial preparations. The focus was set on obtaining stable operation of this highly exothermic reaction (Scheme 6) and minimizing the extent of the side reactions.

Table 2. Applications of organolithium flow chemistry

Target product	*Temp. (°C)*	*Residence time (s)*	*mixer/ reactor type*	*Yield (%)*	*Productivity (flowrate)*	*Ref.*
Tramadol	-14 °C (flow)/-40 °C (batch)	17s for flow	CYTOS system (previous CPC)	87	54 g/h	(*25*)
Inhibitor AZD6906	35	13s/90s for 2 steps	T-mixer/ PTFE tube reactor	26	545.6 g for 2 min	(*32*)
Pauciflorol F intermediate	-70	0.003s	Integrated microreactor	81	1.06 g for 5 min operation	(*55*)
TAC-101	0	12.2s for total	Integrated microreactor	good	132 to 194 mg/min	(*58*)
Dihydro-artemisinin	25	30s	Y-shaped micromixer/ XXL-ST-03	98	1.60 kg /h/L	(*45*)
Diflunisal intermediate	60	2s/60s/600s for Lithiation/ borylation/ SuzukiMiyaura cross-coupling	T mixer / PFA tubing reactor	89	1-100 µL/min flowrate	(*65*)
Amitriptyline intermediate	-50	33s	T-shaped micromixer; microtube reactor; tube-in-tube reactor	76	127 mg intermediate /min	(*69*)
(E/Z) - Tamoxifen intermediate	-50	442.2 s	Vapourtec E-series	96	12.43 g product /80 min	(*71*)



Scheme 6. Reaction network for DFT/DFBA synthesis

Both DFT and DFBA can be made from the same in-situ generated aryllithium intermediate (Scheme 6). DFT results if the organolithium intermediate reacts with dimethylsulfate (DMS) while DFBA is the product if DMF is added.

Deprotonation by a lithium base followed by reaction with an electrophile is a general class of a chemical process for functionalizing an aromatic ring (Scheme 1). Substituted difluorobenzenes, for example DFT, have been made on large scale in this manner. DFT is a valuable intermediate with applications in pharmaceutical, crop protection and electronics industries. It is therefore of interest to find industrially utilizable and inexpensive processes for preparing these difluorobenzene derivatives.

Laboratory methods for the preparation of 2,3-difluorophenyl components (benzaldehydes, arylcarbinols and acetophenones) by means of batch synthesis are known (*76*). But the principle drawback of existing chemistry is the formation of 2,3-difluorophenyllithium as an unstable intermediate. This compound tends to exothermically decompose above a certain temperature. This both deteriorates the quality of the product and produces a dangerous situation should warming of the contents become irreversible.

To avoid such a hazard, Reifenrath and Stiasny (*77*) described a continuous reaction for preparing aryl-metal compounds and their reaction with electrophiles. The advantage of the described two-stage process is from the use of a relatively small reactor volume in conjunction with a continuous reaction, thus only small amounts of the unstable intermediates are ever present in the reactor.

From a safety point of view, it is even acceptable to operate the reactor above the decomposition temperature as the intermediate does not decay very quickly. Consequently, lower production costs result if non-cryogenic equipment is not required. A further advantage is that at the higher temperatures now possible, an increase in the reaction rate takes place so that it may be possible to use less reactive aromatics. With regard to the temperature, Reifenrath and Stiasny have also (*77*) described an organolithium process that is performed at temperatures above -40 °C. Based on this literature information a two-stage technology (Figure 10) has been selected for further development.

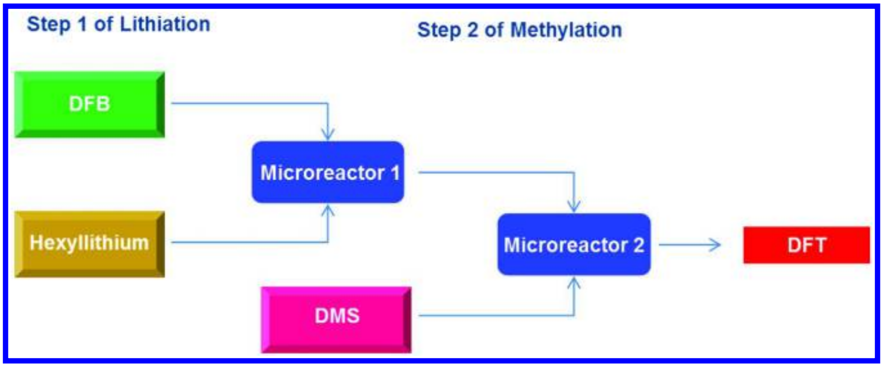


Figure 10. A 2-step MRT process for the synthesis of DFT for a liquid crystal intermediate

Scalable Modules for Flow Chemistry

A large variety of modules are available for performing reactions in continuous mode. There are home-made T-junctions up to carefully fabricated micron-scale channel based modules made from quartz, silicon or steel (*18*, *78*). The majority of these devices have been developed for small scale applications in chemical laboratories. However, for the development of processes for commercial application, the laboratory scale hardware should be suitable as models for scale up. Some commercially available (*79*) MRT modules cover flows from 0.05 to 10000 L/h. In the following section, we will introduce several selected modules that were applied to the development of the process to produce DFT.

Modules Selection

One of the major obstacles for the application of MRT in lithiation reactions is the plugging of the mixers or micro-channels by solids forming during the reactions. Mixers that are resistant against plugging are necessary. The Ehrfeld Mikrotechnik BTS GmbH (EMB) system (*79*) offers two types of micro-mixers that are not susceptible to plugging, the cascade mixer and the valve mixer. The valve mixer operates on the basis of the multi-lamination principle whereas the cascade mixer uses the spilt-and-recombine principle (Figure 11). In the multi-lamination system, the two fluid streams are split into a number of lamellae, which then are interwoven and stacked back into each other like a deck of cards after shuffling. In the valve mixer, one of the fluid components creates a thin film on a conically shaped stamp that is fitted with a spring on the shaft. The second fluid is injected via a ring structure with metal slits creating fluidic lamellae. The force of the flow keeps the channels open. In case a blockage occurs, the spring pushes back the shaft and cone thus closing off the inlets to prevent particles from re-entering the microstructure. This mixer is therefore well suited to systems in which particles may exist.

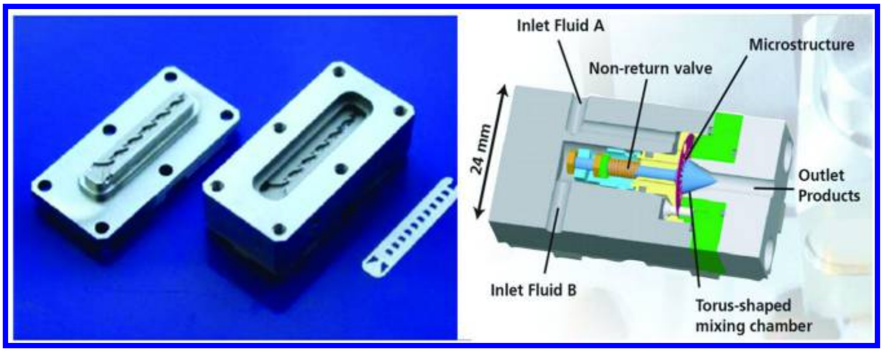


Figure 11. Opened cascade type mixer for the MMRS with schematic illustration of the splitting and recombination of fluidic sections (left) and schematic of the internal construction of the valve mixer (right). Courtesy of EMB (80).

If mixing of high viscosity media is required or if particles are present in the reaction mixture, we use a cascade type mixer. This mixer features a mixing structure (Figure 11) and comprises a row of “kinks” that guide the fluids over cascades whilst splitting the flow horizontally after every change in direction. When looking at the cross section of the mixing structure, one starts off with two different components side by side. The cross section is then split horizontally while the lower part is directed left and upwards and the other part right and downwards thus creating four fluidic threads that are than placed next to each other and pushed together.

Kinetically controlled reactions require residence times in the range of minutes with effective heat removal. This is especially valid for fast and highly exothermic lithiation reactions that require effective temperature control for the application of MRT. For this kind of application, there are the Meander and Lonza FlowPlate™ modules. In both reactor types fluid flows in millimeter sized channels, i.e. it is not a pure microreaction technology. The channel geometry is used to improve the radial mixing of the fluid. Since channels are free of inserts, these reactors can even process suspensions. Fluid in the channels is tempered by the heat exchange through a wall.

Alternatively, for kinetically controlled liquid-phase reactions, Miprowa® modules are useful. The general design concept of this device is based on shell-and-tube construction in the manner of a heat exchanger but with rectangular tubes and exchangeable mixing structures (Figure 12). Through this channel geometry, the device offers a relatively large area to volume ratio whilst the static mixing inserts provide intensive cross-mixing coupled with good heat exchange in the product channel, even at extremely low flow velocities. The additional advantage of this approach is the ease of cleaning and maintenance of the inserts because they can be readily removed and returned back to the channels. Due to its relatively high surface area, the structural length of a Miprowa device can be significantly shorter than a conventional tubular heat exchanger leading to smaller and more compact devices. Besides an increased area-to-volume ratio compared to the analogous circular channel modules, the rectangular geometry allows the inexpensive manufacturing of inserts using straightforward laser cutting of the structures out of metal sheets. Different inserts with different tooth angles and different tooth densities can be used to accurately adjust the pressure drop, the heat transfer rate, the surface/volume-ratio and the mixing intensity of the apparatus.

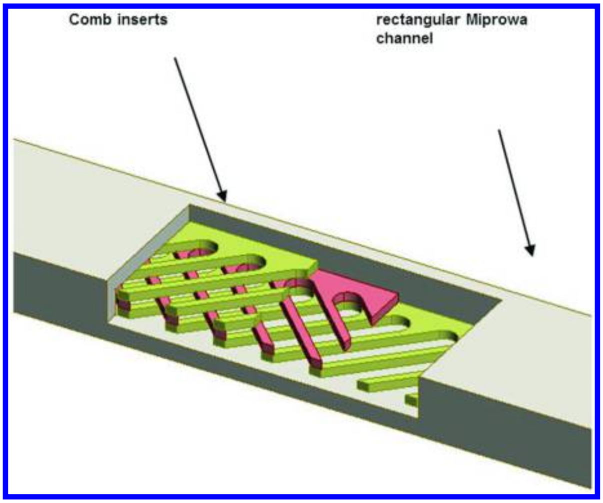


Figure 12. Design principle of the Miprowa® modules. Courtesy of EMB (80).

The compact design of the Miprowa technology and its channels allows realizable scale-up options within three dimensions (Figure 13). The first option is to undertake a sort of numbering-up strategy whereby the number of channels within an apparatus is increased. In the case of the Lab module, this is most easily realized by just changing the end flange. When going from laboratory scale to pilot or production scale, the channel dimensions are sized up as the second scale up strategy. The standard cross section for the channels are either 1.5 x 12 mm^2 for laboratory use or 3 x 18 mm^2 for pilot or production scale. Some other channel widths are also possible for specialized applications, but the channel height will remain at a maximum of 3 mm so as not to lose the beneficial heat transfer characteristics. Typical channel lengths are 300, 600, or 1200 mm. Finally there is always the option to employ several apparatuses in series in a traditional numbering-up strategy.

Figure 13. Scale-up of the Miprowa® technology. Courtesy of EMB (80).

Module Characterization

It has been postulated that MRT based technologies can be easily scaled-up by numbering up. This approach works well only if all geometrical and hydrodynamic parameters are the same across laboratory and commercial scale. In many cases, due to restrictions in the available equipment, these parameters are not the same at different scales. Therefore, the effect of the changing geometry or reaction conditions on the mixing, residence-time distribution and heat transfer should be known. For illustration purposes, selected characteristics that have been determined for the Miprowa modules will be presented. Measurement of hydrodynamic properties of other modules can be found in the literature, e.g. Rodemund et al. (*80*).

Measurements of heat transfer confirmed the ability of the Miprowa modules to possess efficient heat removal characteristics (Figure 14). The overall heat-transfer coefficients vary between 1500 and 4500 W/(m^2K). According to expectations, the heat transfer coefficient increases with the flow rate of process and service media used for heat removal. The dependence of the heat transfer coefficient on the process flow rate on the process side is quite flat since increase of the flow rate by factor of 8 caused only approximately doubling of the coefficient. Accordingly, controllability of the temperature is largely independent of the flow rate. Even higher heat-transfer coefficients could be achieved when operation at very high fluid velocities is used. For instance, for water flowing with velocity of 0.4 m/s, heat exchange coefficients up to 7000 W/(m^2K) have been achieved (*81*).

Very efficient heat exchange has been confirmed for fluids with a variety of viscosities. For instance, coefficients in the range of 2500 W/(m^2K) have been measured at 90 °C and fluid velocity of 0.1 m/s for glycerol which has at normal conditions a viscosity of ca. 1000 mPa·s. It is important that effective heat exchange is valid in wide range of viscosities since the presence of solids increases the effective viscosity and, in turn, negatively impacts heat transfer. Therefore, formation of salts can lead to poorer heat removal and deleterious effects upon the reaction mixture.

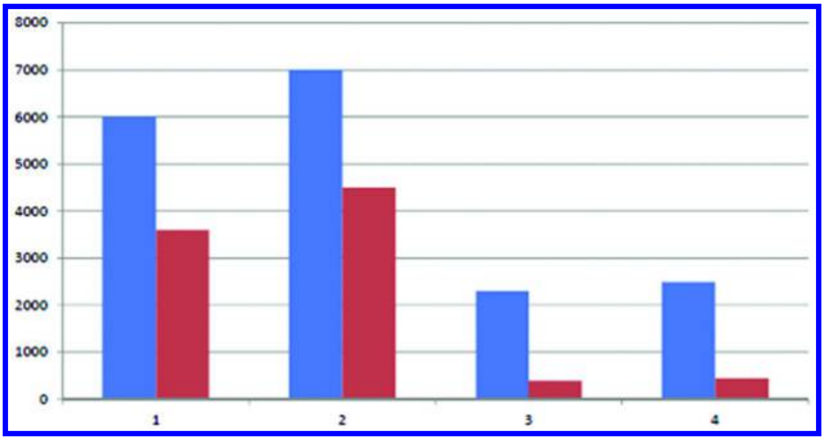


Figure 14. Heat transfer coefficients (W/m^2K) in a tubular reactor with layered inserts ($L=99$ mm, $A= 7.6$ mm^2) as left column and in the capillary heat exchanger ($L=99$ mm, $A= 7.1$ mm^2) as right column, respectively for water ($\eta=$ ca. 1mPa·s, $u=0.4$ m/s)) and glycerine ($\eta=$ ca. 1000 mPa·s, $u=0.1$ m/s): (1) water @ 60°C, (2) water @ 90°C, (3) glycerine @ 60°C, (4) glycerine @ 90°C, after (81).

The heat transfer in the Miprowa design is significantly enhanced by the inserts in the open channel as it significantly raises heat-transfer coefficients to the range of 1000-1500 W/(m^2K). Obviously, the mixing elements raise the heat transfer capacity by a factor of 2.5-3. Heat transfer characteristics that had been determined experimentally for various fluids and temperatures was used to elaborate a model that allowed prediction of thermal characteristics of modules with different design of inserts. The heat exchange characteristics in the Miprowa module is similar to those incorporating ribbed heat exchangers.

In most reactor networks, selectivity depends on the residence-time distribution (RTD). In general, a narrow RTD is preferred. Results of the RTD measurements in a laboratory Miprowa unit that have been performed with tracer pulse technique are presented in Figure 15. The measured distribution is significantly improved as compared to laminar flow. It can also be clearly shown that the inserts inside the channels cause a significant narrowing of the residence time distribution. Furthermore, this distribution is quite insensitive to the flow rate.

Development of the Technology for Aryl Methylation

Methodology

Technological development was performed in two stages. In the first stage, experiments were carried out in the laboratory unit (Figure 16). This is a general purpose experimental setup for performing proof-of-principle experiments.

After the typical safety analysis for introducing lab scale work using potentially hazardous chemicals, e.g. DTA, operation was limited to a few hours and only high purity chemicals were used at 1-100 mL/min flow rates. The unit temperature was controlled by immersing the mixer and modules in a bath with a thermostat attachment. Both EMB laboratory modules and capillaries were utilized (Figure 16). This unit made it easy to modify or to replace the modules in case of plugging but at this stage the optimization of the reaction modules is not the key object. Temperature was measured indirectly via the bath temperature and the reactants were fed into the mixers by HPLC pumps. Flow rates were determined by means of weight loss of the reactant reservoirs.

The central purpose of these experiments was to generate information on kinetics. This would define the window of reaction conditions for stable operation, provide primary information on the maximum yield, the space-time-yield and will allow the identification of by-products. In these studies, about 100 g of DFT was synthesized for testing its quality.

Based on the evaluation of the data from these laboratory-scale studies, the most promising conditions were identified and further studied in the pilot unit (Figure 17). The purpose of this pilot unit study (capacity in the range of 1 to 60 L/h) was to test the reaction over long term operation. The primary goals were:

- identifying the hardware configuration for stable operation
- defining reaction conditions for stable operation
- confirming the chemical performance identified in the laboratory experiments

Furthermore, the robustness of the identified optimal reaction conditions would be confirmed by the preparation of 10 to 1000 kg of product.

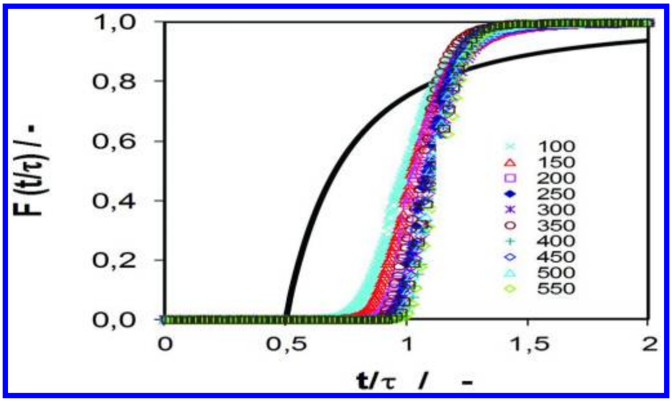


Figure 15. Residence time distribution in the Miprowa® type modules. Module dimensions: 11,4 x 6 x 1000, VL= 55 ml, flow rates in mL/h.

Figure 16. Laboratory MRT unit for initial studies

Figure 17. Pilot plant DFT unit

The Piping & Instrument Diagram (PID) of the pilot unit (Figure 18) illustrates its complexity which is comparable with that of a chemical plant. The pilot-scale unit can be divided into several blocks. The first one contains tanks with the feedstocks, the second one are pumps and heat exchangers to pre-temper reactants, the third one is the reaction block, and the fourth one consists of containers to receive off- spec and acceptable product solutions. Finally, the chiller with the cooling loops forms the last block. This cooling system allowed independent temperature control in different modules for maximum efficiency.

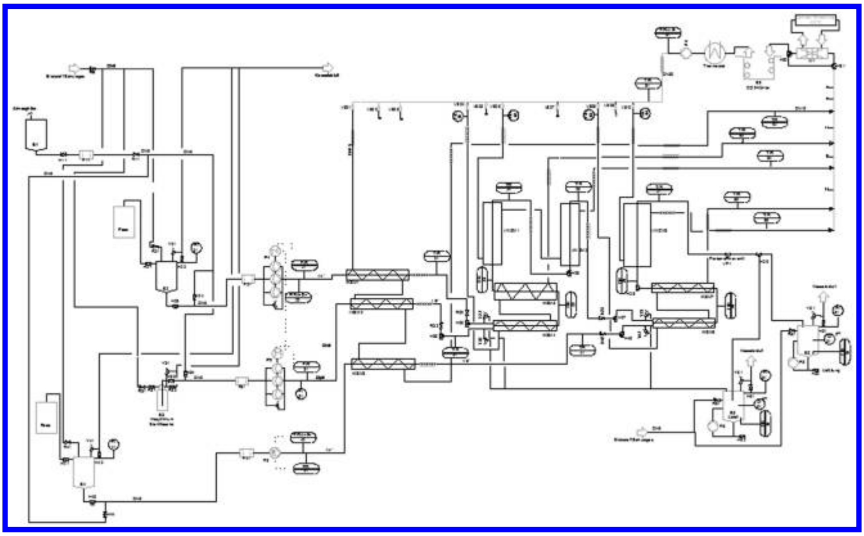


Figure 18. PID chart for pilot plant DFT unit

Only the reaction block is based upon MRT technology; the rest has been designed from standard chemical equipment and the best practices from the fine-chemicals industry. All containers were vented with inert gas. Since technical grades chemicals are now used, guard filters were used to eliminate particulates in the reactant lines. In order to minimize pulsations in the stream, parallel piston-membrane pumps were used and flow rate controlled using coriolis-flowmeters. Pressure was monitored with the aim to detect plugging when it occurred. Temperature was measured directly in the product stream either in or directly behind the module. The reaction block was placed in a movable rig (Figure 17), however note that this picture shows the stainless steel lines before they have been insulated and hidden from view. In this pilot plant, there was no critical requirement for corrosion protection; only sealing material had to be adapted to low temperatures.

The flexible design of the reaction rack allowed the testing of different types of modules. They may be connected directly using tubes or attached to the base plate of the EMB system which allowed clamping and a direct connection of various modules (Figure 19). Furthermore, this set-up avoids excessive fittings and tubing between module functionalities and therefore the total and dead volumes are minimized. This issue is critical for fast, highly exothermic reactions in order to eliminate sections that are not actively cooled that can lead to hot-spots. Operation of the pilot unit is controlled by a dedicated control system which was also responsible for data acquisition and alarms. The control system also initiates emergency procedures such as shut-downs.

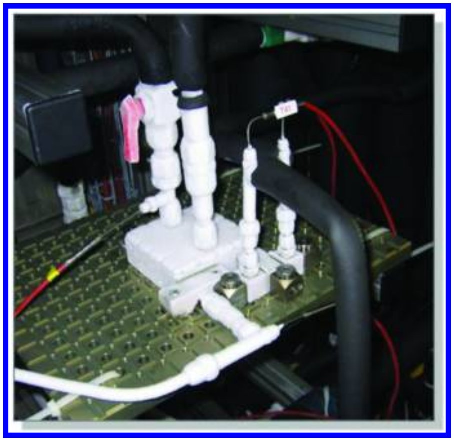


Figure 19. EMB base plate with the mounted modules

Results of the DFT Studies

Laboratory experiments confirmed the value of MRT technology for this reaction class. The studies were performed in 30 mL reactors at 20 g/h at -45 °C. The reaction could be performed safely at a temperature nearly as high as the decomposition temperature of ~ -30 °C. There was a significant difference between the rates of the two reaction stages. The residence time for the quantitative conversion to organolithium intermediate in the first step was 2-4 min but the subsequent step (reaction with dimethylsulfate) was completed in only 4 s at -45 °C. Under these conditions, a selectivity of up to 97% was achieved due to a possible slight decomposition of organolithium intermediate. Based on these promising results, further development moved into the pilot plant.

In the plant however, problems occurred with obtaining stable operation due to plugging from precipitated solid particles. This plugging occurred in different parts of the unit, but it was primarily located at both micro-mixers. It should be mentioned that predicting plugging from the laboratory studies was not obvious. Pressure increase is the primary indicator, however pressure measurement due to solids deposition is not linear and can be hard to detect in the initial stages. Usually there is a long preliminary period with only a slight increase of pressure as particles deposit on the walls. Over time, particles start to block a significant cross section of the channel and pressure rises quickly. The process culminates in the total blockage of the channels.

Plugging can be attributed to multiple factors, but mainly due to the poor solubility of some lithium species from high concentration and low temperature

(< -55 °C). The primary culprit was the precipitation of the intermediate product difluorophenyl lithium (DFPL) formed in the first stage. Then up to – 33 °C, another problem is the precipitation of lithium methylsulfate ($LiMeSO_4$) which forms in the second stage. Above -30 °C, formation of solid particles occurs due to the decomposition of the organolithium intermediate leading to the daughter byproducts such as LiF. Finally, LiOH can form as the product of reaction of hexylithium with traces of water. The last problem has been controlled by the use of molecular sieves to dry the solvents. Other sources of plugging have been addressed by two ways: selection of better module configuration and optimization of reaction conditions.

In the initial design, the multi-lamination mixers were used. However, it was necessary to replace them due to the plugging of lamellas. The best performance was achieved with the cascade mixer as it can deal with slurries. Since the reaction was not very fast, this mixer was followed by a Miprowa module or another effective heat exchanger. For the second stage, the valve mixer was added. This mixer is insensitive to particles formed during the mixing. However, this meant that an efficient heat exchange module like the Meander reactor or the Miprowa had to be attached to the mixer. Sufficient residence time at tempered conditions had to be allowed in order to prevent unreacted feedstock to continue to react in the product tank.

These secondary remedial measures were combined with a program of optimization of reaction conditions (*37*). We determined that for the first process step, the best parameters are a reactor temperature between 55 °C and -45 °C with a residence time of 3 to 5 min. A temperature window of -55 °C to -45 °C constituted an optimum range as regards minimal decomposition while still permitting sufficient solubility for the lithium intermediate formed. We also discovered that the best conditions for the addition of the electrophile in the second reaction stage are carried out at higher temperatures: between -40 °C and -30 °C using residence times of 1 - 10 sec. This finding confirms the necessity for independent temperature control at both stages and established our reactions conditions.

In the pilot plant studies, the value of MRT technology for this lithiation reaction was confirmed. A total of 100 kg of 2,3-difluorotoluene isolated as a 10 wt % solution was synthesized. The MRT technology was superior with respect to the batch process as the selectivity was 94 % as compared to 90 % in the batch operation, because less organolithium intermediate were decomposed due to improved control of reaction temperatures with MRT. As ~ 40 kg of product were made in 24 h in equipment with a total volume of 3 L, the space-time-yield for the MRT unit was also superior to the batch reactor which consisted of a volume of 400 L producing only 20 kg of product over 24 h. A third advantage was the avoidance of cryogenic conditions. The batch reactor required a temperature at least as low as -70 °C to avoid decomposition as compared to an average of -45 °C in the MRT. This difference is largely defined by the safety margin required to avoid product decomposition in the stirred tank reactor. Correspondingly, the cooling equipment is more complex for the batch system due to its size.

However, the greatest advantages to flow are realized in the improved process safety achieved. During the MRT operation, the small volume needed meant the equipment can be easily secured and reaction conditions such as pressure and temperature are well controlled. Due to the small hold-up of solution, it responds quickly to corrective actions and the risk potential of thermal events are lower. Therefore, only a small dump tank is necessary in case of problems where everything can be quenched quickly. For a batch system, sophisticated safety considerations are necessary and a means to quench the entire reactor volume has to be available in stand-by.

Production Unit – Engineering and Performance

Based on the experience collected with the pilot unit, a dedicated MRT facility for commercial operation was designed and built. The engineering concept was designed for industrial application to handle relatively fast exothermic reactions that were to be held at low temperature. Examples of organolithium reactions that would be first run were the production of 2,3-difluorotoluene (DFT, (*37*)), 2,3-difluorobenzaldehyde (DFBA, (*38*)) and 2,3-difluorophenylboronic acid (*39*). This facility would be designed for industrial manufacturing with a designed production capacity of up to ~150 tons/year.

In the manufacturing unit, three reactants could be fed with flow rates up to 0-18 L/h while the reaction temperature could be held as low as -45 °C. Operating pressure could be varied between up to 12 bar. The facility had been constructed applying industrial standards, including a skid-mounted reaction unit (Figure 20), raw material supply, product storage and an auxiliary cryogenic cooling system. In addition, it was equipped to supply external nitrogen, compressed air and cooling water. Reactants were stored in separated, pressurized tanks. All the equipment for the core system were integrated into the skid to be movable. It had a compact structure with a modular architecture so that the system would be easy to disassemble, clean and re-assemble with a footprint of only 2 m^2.

The skid was divided into the reaction and the control parts. The reaction part was closed and vented with nitrogen. The control section was integrated and contained the operations of data acquisition, direct digital control, alarms and safety procedures. The control system was based on the LabVIEW platform (*82*). This allowed automatized operation and offered graphical representation of process data for current operation, e.g. real-time trends as well as historical trends. Control functions included advanced PID control but also start-up and shut-down procedures. Alarms with built-in emergency procedures could activate flushing procedures to remove potential hazardous mixtures in the reaction system and as well as in the waste receiving vessel. Pressure was carefully monitored in order to quickly locate plugging in the reactors in order to react to such problems. In the case of a malfunction leading to a temperature increase reaching levels with a danger of decomposition, the internally integrated overflow device (pressure release valves) would be activated to disperse the heat directly.

Figure 20. Manufacturing unit

Equipment arrangements are visualized in the control system's screen (Figure 21). Reactants are supplied using industrial standard pumps connected to Swagelok insulated tubing and valves. Since the maximum pressure was restricted, pumps were equipped with an internal overflow device function. The tube volumes and residence time (~10 sec) had been minimized to maintain controlled reactions. Flow rates were regulated by means of the autonomous mass flow controllers. Set points were communicated from the control computer. The reactant's temperature was tempered in the micro-structured heat exchangers before entering the micro-reactor.

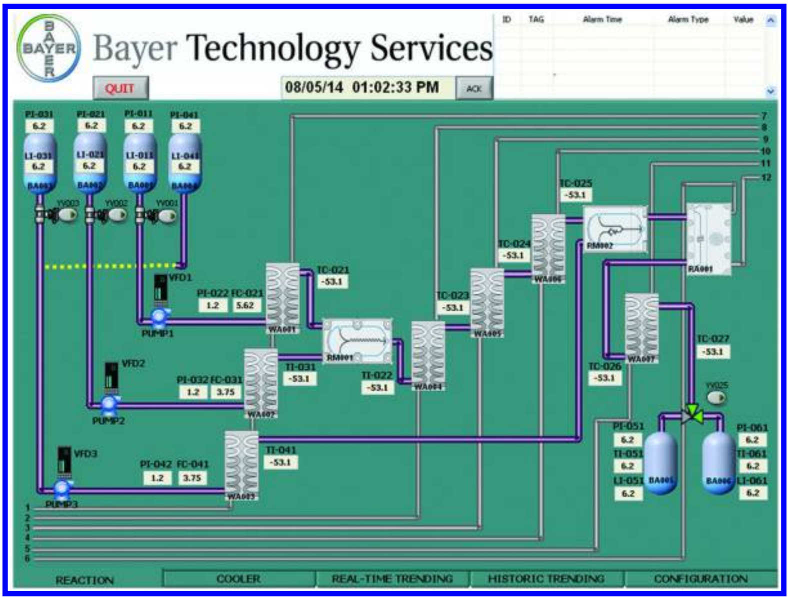


Figure 21. Screen shot of the control system showing system configuration

In order to achieve extended residence times of minutes, tempered delay modules were used. Automatic control of reaction temperature was realized by means of direct digital control. Temperatures were controlled by the flow rates of the refrigerant.

Performance of this unit can be illustrated by the results obtained for making 2,3-difluorobenzaldehyde (DFBA) (Scheme 6) starting from the feed stocks: 1,2-difluorobenzene (DFB), *n*-hexyllithium (33% wt in hexane), *N*,*N*-dimethylformamide (DMF) and tetrahydrofuran. DFB was first lithiated by hexyllithium at -45 ºC to produce the aryllithium intermediate DFPL, followed by the nucleophilic reaction with DMF to produce DFBA in solution (*38*). The reaction mixture was then neutralized with a slightly acidic aqueous solution under agitation.

The reaction rate in the first reaction step was slower so the residence time in this step varied between 2-4 min. Stable operation was achieved by the large heat exchange area to absorb the reaction enthalpy of 230 kJ/mol. In Figure 22 temperatures for the first step reaction over an 11 h campaign are presented. This diagram illustrates that stable operation for the first step with excellent temperature control was achieved.

More challenging was the second step. The high reaction enthalpy of 480 kJ/mol and the residence time of 4 s mean that more than double the amount of heat was released only in a few seconds. Therefore, not only a sufficient heat exchange area was required, but also a high heat exchange coefficient was necessary in order to prevent an unacceptable temperature rise that may lead to run-away reaction. The steady line recorded in Figure 22 illustrates that the unit is very fast to respond to changes in temperature.

The experience obtained in the commercial unit (*38*) was in line with the previously reported investigations in the pilot unit (*37*). The success of the entire process was the natural consequence of a good balance of temperature, concentration (solubility) and pH control (quenching step) leading to excellent yield, high selectivity and impurity control (Scheme 7).

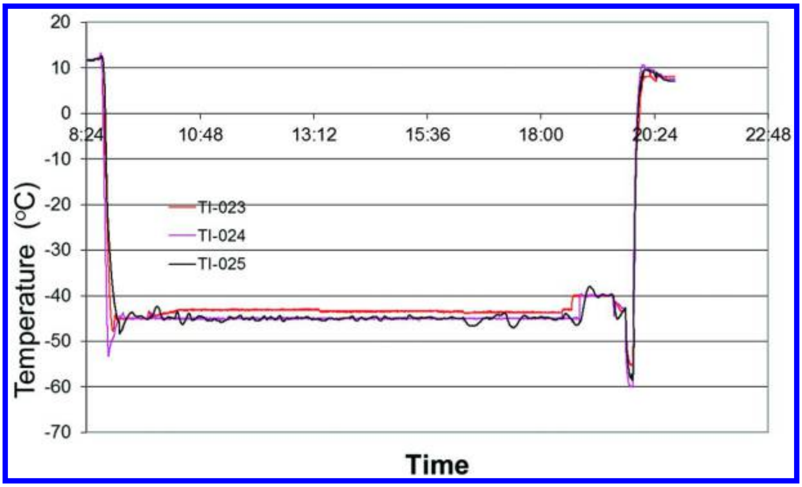
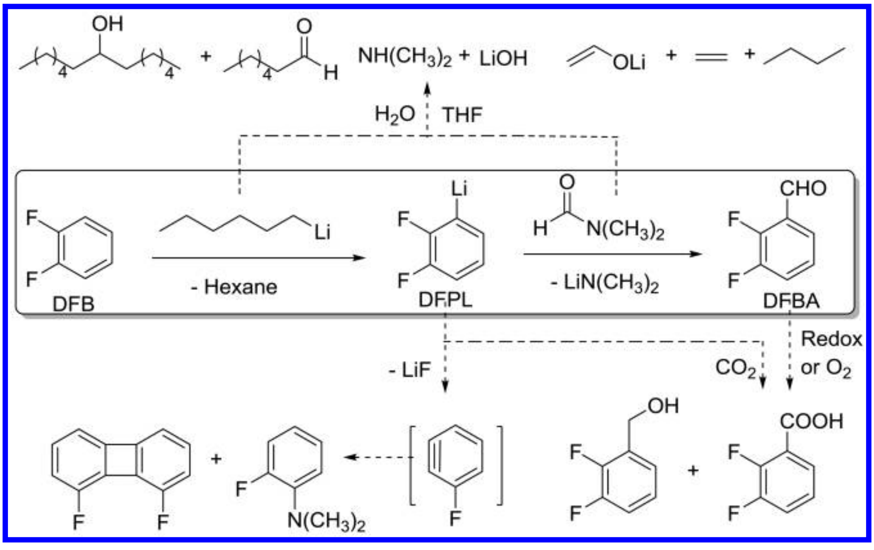


Figure 22. Temperatures in the micro-reactors during operation, with the location of the temperature measurement points TI-023 – TI-025 given in Figure 21. Conditions: 12% DFB/THF, 33% HexylLi, 20% DMF/THF, residence time between 3.7 min to 4.5 min



Scheme 7. The 2-step synthesis of DFBA and possible side reactions leading to impurities.

In regards to important parameters, the process should be run under moisture and air-free conditions because both hexyllithium (HexLi) and the key intermediate DFPL are highly sensitive to moisture or air. If water exists in the first step (micromixer/reactor, DFB feedstock or solvent), the side reaction will lead to the incomplete conversion of DFB. If the second step is contaminated by water (micromixer/reactor, DMF feedstock or solvent), then the conversion will be decreased as the starting material, DFB, would be regenerated. In the case of air contamination in the system, usually difluorobenzoic acid byproduct would be produced from either the combination of DFPL and CO_2 or the oxidation of DFBA by O_2. Therefore, careful preparation is necessary to assure that neither water nor air contaminates in the reactions. To our expectations, these impurities did not present problems in our process.

The second key factor is maintaining a low reaction temperature because many side reactions will occur when it exceeds a critical reaction temperature (-35 ºC). The DFPL intermediate (*83*) is very sensitive to temperatures above -35 ºC and would eliminate LiF to form benzyne (Scheme 7). Benzyne derived products have been detected (*84*) during some nucleophilic substitution reactions on aromatic rings. Sometimes malfunctions or hot-spots may produce various benzyne side reactions such as reaction with nucleophiles (here $LiN(CH_3)_2$) or electrophiles, or it may undergo pericyclic reactions.

In addition, a side reaction will occur between HexLi and THF near room temperature (*85*) wherein THF loses a proton and cleaves to ethylene and the anion of acetaldehyde (Scheme 7), although it is not a rapid reaction under normal operation conditions. We did not note its occurrence.

The control of pH and temperature was important in minimizing side reactions during the quenching/neutralization step. The non-enolizable aldehyde DFBA, may undergo a Cannizzaro reaction (*86*) at room temperature under relatively strong basic conditions to form the corresponding carboxylic acid and alcohol. Although this side reaction was not a problem at low temperatures, it could become significant at higher concentrations of base and during the quenching step as the temperature gradually increases.

Finally, the molar ratio among those three reactants will impact the impurity profile and yield. For instance, the side reaction between HexLi and DMF can give multiple byproducts even at low temperature if the first step of the reaction is incomplete or if both HexLi and DMF are present in excess. Thus, it is recommended to use nearly the stoichiometric amounts of both HexLi and DMF in order to facilitate the following isolation/purification process by producing less byproducts.

As shown in Table 3, DFBA production between 1.5 and 2 kg/h was achieved with all conversions above 95%. A higher temperature (-40 ºC) increased the yield obtained from either 12% or 15% DFB/THF as feed stocks. The selectivity was nearly constant between -45 to -40 ºC. One of the best runs produced an 85% yield of product DFBA (with 89% selectivity) at a conversion of 96% of DFB.

Table 3. Chemical performance in the demonstration unit for 12% DFB/THF[a]

DFB/THF	*33% HexLi*	*20wt % DMF*	*Temp. (°C)*	*Conv*	*Selec*	*Yield*	*Capacity of DFBA (kg/h)*
Flowrate (kg/h)	*Flow rate (kg/h)*	*Flow rate (kg/h)*					
14.85	4.8	7.42	-40	97%	87%	84%	1.87
14.85	4.8	7.42	-45	95%	88%	83%	1.84
13.6	4.395	6.8	-45	96%	88%	84%	1.72
12.09	3.91	6.045	-45	96%	89%	85%	1.54

[a] Note: Data are the average results of several trials. The term ‘selectivity’ refers to the percent of desired reaction divided by all reactions that occur in that step.

Conclusions

In the last decade novel production concepts exploring continuous processing for chemical and pharmaceutical manufacture have been pursued. This development is no longer driven solely by academia. Initiatives and corporate programs led by chemical and pharmaceutical companies have been formed with the aim of developing alternative technologies (*87–89*) to address changing market demands (*90*, *91*). A key aspect of this development are modular chemical production plants (*22*, *92*) driven by the possibility of accelerated process and product development (*93*). Early expectations were that a direct scale-up of flow chemistry from the laboratory to a first production unit would be possible and this could be subsequently expanded by numbering up. Alternatively, the development of new processes on the basis of flow chemistry has been achieved by applying classical chemical engineering rules to produce a conceptually new approach.

However, this approach will be competitive only when developmental workflows and the corresponding experimental hardware are available. Bayer Technical Services has developed the corresponding workflow and the necessary infrastructure along with suitable equipment to enable the preparation of fluorinated organolithium intermediates. The whole development concept was based on scalable modules that are flexible and inexpensive to fabricate. For fast and reliable development, resources and expertise from various disciplines including synthetic chemistry, kinetics, mixing, heat transfer, safety, equipment, infrastructure, process design and engineering, and technology evaluation must work together efficiently.

However, the use of MRT and FC is not a silver bullet; these technologies bring advantages only when the target reactions meet certain criteria. Generally speaking, MRT and FC technologies are advantageous primarily for hazardous reactions, very fast reactions, complex reactions where selectivity is required, novel process windows and micro-mixing controlled reactions. These criteria are discussed in the literature (e.g. (*19*, *22*)) and must be carefully considered before embarking on new initiatives. Certainly, organolithium chemistry belongs in this grouping, as we have demonstrated. This work has shown that laboratory studies (*7*) can be transferred into industrial scale operations and retain all the advantages seen in the laboratory. In all important aspects, continuous lithiation of fluoroaromatics was superior to the batch process. Furthermore, the MRT technology was quite flexible within the one reaction class as the production of one intermediate (difluorophenyllithium) could be used to make two different products (difluorotoluene and difluorobenzaldehyde).

The biggest challenge to perform lithiation reactions in the flow mode in the MRT equipment was the precipitation of solids. It was addressed by the selection of suitable hardware and optimization of reaction conditions. Nevertheless, other measures like clean-in-place concepts that have been already successfully applied in commercial MRT based units (*94*) can be examined in order to increase robustness of this technology further. The field of continuous processing is expected to continue demonstrating innovation for a long time to come.

Acknowledgments

The development of this work required several years and a large number of scientists and engineers were involved. It is impossible to name all of them. However, we wish to thank the main contributors: Stephan Laue, Verena Haverkamp, Peter Jähn, Thomas Runowski, Fengdong Yu, Daishi Guo and Tao Liu. Our thanks go to all of them.

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Chapter 16

Continuous Flow Chemistry of Metal Mediated Carboxylation and α-Arylation Reactions

Sripathy Venkatraman,* Scott Tweedie, Mark McLaws, and David Lathbury

AMRI, 26 Corporate Circle, Albany, New York 12212
***E-mail: Sripathy.Venkatraman@amriglobal.com**

Utility of continuous flow chemistry in a carboxylation reaction and palladium-mediated α-arylation reaction is described. A two-step carboxylation reaction of an aryl group involving an anion formation, followed by quench with gaseous carbon dioxide was developed on small scale using HDPE tubes in a dry ice/acetone bath. The process was then scaled up using stainless steel tubes of larger diameter and static mixers to process 22 kg of material in a regular lab in 88% yield. Similarly, a continuous flow process for a hazardous palladium-mediated α-arylation reaction which had a significant exotherm during heat up was developed.

Introduction

Metal-mediated reactions are synthetically useful and widely employed reactions in the pharmaceutical industry. In the last century, significant advances have been made in this field (*1*) and as a result, it has been possible to develop processes utilizing these methodologies to produce API's and key intermediates on large scale. Most commonly used in industry are the Barbier-Grignard type addition reactions, palladium-catalyzed coupling reactions and metal catalyzed oxidation and reduction reactions.

Many of these reactions are associated with potential safety hazards (*2*). For example, the organometallic species formed from Barbier-Grignard type reactions are known to have the propensity to violently take off (*3*). Palladium-catalyzed Suzuki and Heck reactions are known to initiate only at high temperatures and the rapid energy release at that temperature could be sufficient to boil off reaction solvents. In spite of these potential hazards, it is common to perform these reactions in batch mode. However, extensive safety studies need to be conducted during process optimization to avoid potential runaway situations. Thus, owing to the advantages offered by these reactions, a significant amount of time and energy is routinely spent on understanding the safety and hazards of these reactions to minimize risks on large scale.

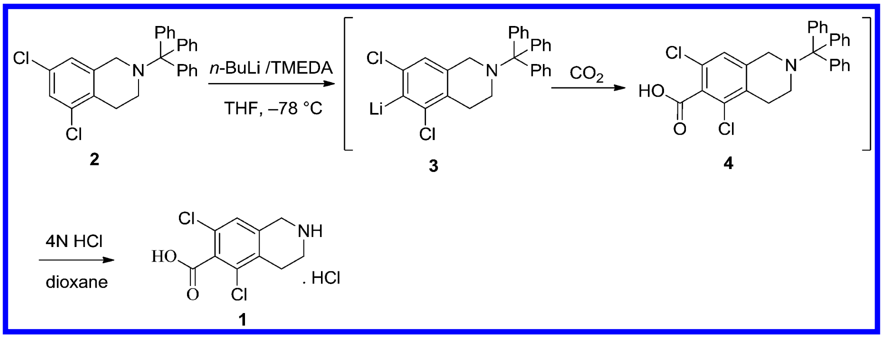
Recently, continuous flow processes have received attention as alternatives to batch and semi-batch processes (*4*). This is a very attractive development especially in regard to conducting hazardous chemistry. In addition to high mixing efficiency and excellent heat transfer capacity under flow conditions, the volume of the active reaction mixture is small at all times and in the event of an uncontrolled reaction, the impact and consequences are correspondingly small. At AMRI, continuous flow chemistry is routinely evaluated for such hazardous reactions (*5*). We will discuss two examples from our experience that will provide a useful example for others to consider when transitioning from a batch reaction to a flow modification.

Discussion

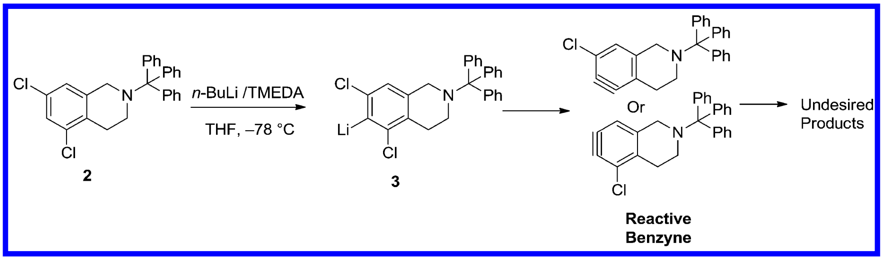
Continuous Kilogram Scale Process of a Carboxylation Reaction

Incorporation of a carboxyl acid into an aryl group by the addition of carbon dioxide (CO_2) to a Grignard or lithium carbanion is a well-known transformation that is widely used in chemical and pharmaceutical industries (*6*). In general, most of these reactions are carried out in semi-batch mode at low temperatures by the slow addition of gaseous CO_2 to the carbanion. However, temperature excursions during carbon dioxide quench due to inefficient heat transfer can often lead to multiple by-products.

Compound **1** (Scheme 1) is an intermediate used in the preparation of an API at AMRI (*7*). The carboxylic acid **1** was prepared by the addition of CO_2 to the aryl lithium **3** generated from **2** at -78 °C in 75% yield. The reaction was sensitive to temperature and the yields were much lower on larger scales where heat control was less efficient resulting in significant amounts of dark tarry materials. In addition, several impurities were formed at higher temperatures (>-65 °C) that made purification extremely difficult. *o*-Haloaryl lithium compounds, such as **3**, are known to form unstable benzyne (*8*) type intermediates (Scheme 2) which can decompose rapidly or lead to non-productive reactions. On scale, such a situation can be also become hazardous as well as impacting quality.



*Scheme 1. Synthesis of Compound **1***



Scheme 2. Formation of Benzyne Intermediates leading to Decomposition

To overcome the problems of explosive compounds and unstable intermediates on scale, a continuous flow approach for large scale preparation of **1** was envisioned (*9*). The batch procedure for the carboxylation reaction involved the addition of BuLi (2.5 M in hexanes) to a THF solution of **2** in the presence of TMEDA at -78 °C. The resulting aryl lithium **3** was then quenched with gaseous CO_2 followed by protononation to produce the product. In order to avoid temperature spikes with subsurface additions, a blanket of CO_2 was maintained as the means to introduce CO_2. Since an in-process analysis of the anion using off line techniques was not practical, the conversion was monitored after quench with CO_2, introducing a measure of ambiguity into the process. Kinetic studies done in a batch mode on small scale using an in-situ ReactIR probe clearly pointed out that both the anion formation and CO_2 quench were instantaneous.

Design of Flow System

The initial concept of the flow reactor (Figure 1) consisted of three loops (A, B and C) where loop A was used to cool a mixture of **2** and TMEDA in THF to -78 °C. Just after loop A, the base was added and loop B provided the necessary residence time for the anion formation after which CO_2 gas was added which passed through loop C to give the product. The entire reactor was submerged into a dry ice-acetone bath. For the initial evaluation, the loops were made of 1/16th inch high density polyethylene (HDPE) tubing with two HPLC pumps for adding the reagents. The success of this apparatus then allowed confidence to proceed to larger scale.

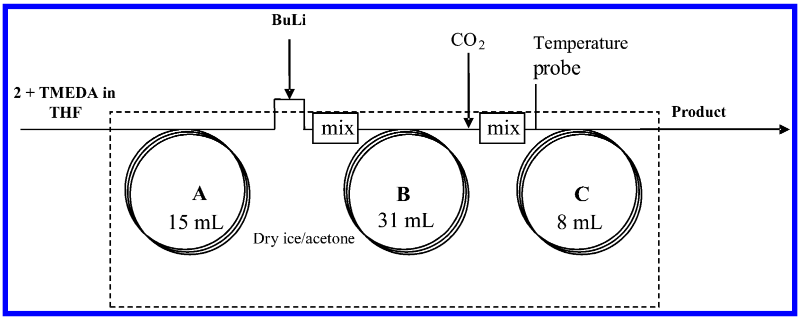


Figure 1. Initial Reactor Design

The larger mixing units consisted of ¼” ID diameter PTFE tubing with two small stir bars encased within the tubing (Figure 2). The stir bars were agitated using a magnetic stir plate in order to provide turbulence sufficient for mixing of the reagents. Carbon dioxide was fed directly from a cylinder at a rate sufficient to provide approximately 4 molar equivalents at completion. The back pressure unit at the end of the product stream was set to 10 psi.

Figure 2. Initial Reactor Set-Up

Optimization Development

The residence times for the trial runs using the 1/16th inch HDPE tubing were based on reaction monitoring in a batch reaction (HPLC analysis). Addition of the base to **2** in THF was marked with a color change from pale orange to dark red, which decolorized upon quench with CO_2. The flow rates were adjusted to achieve a base stoichiometry twice that of starting material (*10*). Running at less than two equivalents led to incomplete reaction. The product stream was directly quenched into 2N HCl after steady stage was achieved, worked up in a batch mode by extracting into isopropyl acetate (IPAc) followed by a solvent swap to dioxane, and then taken to the next step to isolate **1**.

Several experiments were carried out to optimize the flow rates and residence times (Table 1). Increasing the residence time for the CO_2 quench from 1 min to 5 min led to a dramatic increase of 35-41 HPLC area % for the conversion

(*11*). Commercially available 1.5 M BuLi varied significantly in quality from lot to lot and the flow rate had to be adjusted accounting for the lower potency which lacked reproducibility. This issue was overcome by the use of a 2.5 M solution (in hexanes) which was much more consistent in quality. After some experimentation, the conditions were optimized by increasing the concentration of **2** in THF to 10% and lowering the residence time for the anion formation to 10 min. These changes led to a reproducible >90% conversion. We progressed to process larger quantities of material by adapting the same system but using ¼ inch ID HDPE tubing. The conditions optimized for the 1/16th inch tubing were repeated and identical results were obtained.

Table 1. Optimization of the Carboxylation Reaction

Scale (g)	***Concentration of 1 in THF (%)***	***BuLi (M)***	***ID (inches)***	***Residence time (min)***		***Conversion (%area)***
				Anion formation	***CO_2 quench***	
5	6.7	1.5	1/16	17	1	55
5	6.7	1.5	1/16	17	5	90
30	10	2.5	1/16	10	5	93
100	10	2.5	1/4	10	5	96

Scale Up to Kilogram Input Optimization

With the need to produce several kilogram quantities of material plus facing issues of poor heat transfer and leaching in HDPE tube reactors possibly caused by incompatibility with THF, stainless steel tubes were built for larger scale processing. When designing a flow reactor, an important factor to be considered is the minimum tube length at maximum operational flow rate required for complete heat dissipation. If l_1 is the length needed to achieve the desired residence time and l_2 is the length needed for complete heat dissipation, then the tube length is usually decided as the higher of the two. The length l_1 is calculated based on the flow rate and the tube diameter. The length needed for complete heat dissipation (l_2) for a known flow rate can be calculated from the following equation.

$$Q = UA\,\Delta T_{lm}$$

Q – Heat Rate, BTU/hr; Q can be calculated according to the thermal properties of the process fluid (for process that has no reaction going on in the loop) or the enthalpy of the reaction occurred within the loop.

U – Heat Transfer Coefficient, BTU/(h-ft^2-F); U can be obtained according to literature data for known material construction of the tubing and the nature of the heat transfer media and the process fluid in the tubing.

A – Surface area, (ft^2); A can be expressed using the tubing length and the tubing internal diameter.

ΔT_{lm} – logarithmic temperature difference between process fluid (t_{in} and t_{out}) and the coolant (T_{in} and T_{out}), °F

$$\boxed{\Delta T_{lm} = \frac{(t_{in} - T_{out}) - (t_{out} - T_{in})}{\ln\left(\dfrac{t_{in} - T_{out}}{t_{out} - T_{in}}\right)}}$$

Loop A is a cooling loop and as thus, no heat was released from that operation. The length required for loop A to cool from ambient temperature to -78 °C was calculated to be 14 feet. However, for the anion formation step, the heat of the reaction needs to be dissipated (in loop B) before the CO_2 quench (in loop C). If the length of loop B is shorter than the calculated length, the heat released during this reaction will not be completely dissipated with a shorter tube and the carbon dioxide quench may be done at a higher temperature, resulting in unwanted side reactions. The heat of reaction needed for the calculation was obtained by performing an RC1 experiment (ΔH values for each stage summarized in Table 2). Based on the heat that needs to be removed for loops A and B, the minimum length at the maximum flow rate was calculated to be 14 feet and 22 feet, respectively. The exothermic quench with CO_2 produced the need for the longer tube to maintain the reaction at a low enough temperature to avoid problems.

Table 2. Tube Length Calculations

Loop	***Flow Rate (ml/min)***	***U (btu/h-ft^2-F)***	***ΔH (KJ/mol)***	***Q (BTU/hr)***	***A (Ft^2)***	***Length (Ft)***
A (Cooling)	102	10	-	766	1.14	14
B (Anion Formation)	120	10	19.81	282.7	1.8	22
C (CO_2 Quench)	>120	-	42.68	-	-	-

Three stainless steel tubes of 5/16” diameter were built (Figure 3), coiled and immersed into a carboy filled with a dry ice acetone slurry (*12*). Six static mixers (*13*) were inserted into the tubes after both the anion formation and carbon dioxide quench sections to provide the required mixing.

Since mixing using a static mixer was very efficient, it was possible to further reduce the residence and thereby increase the flow rates. Table 3 summarizes details of the scale up runs.

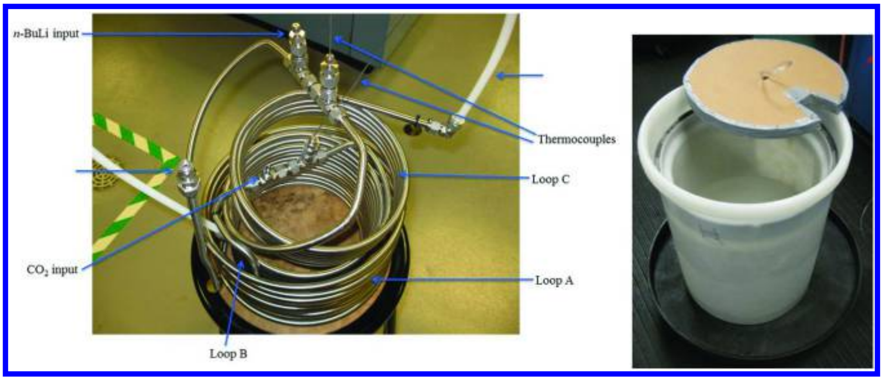


Figure 3. Second Generation Reactor Set-Up

Table 3. Details of Scale-Up Runs to Kilogram Inputs

Entry	*Scale (kg)*	*Residence Time (min)*		*Product HPLC Purity (% area)*	*Yield Over Two Steps to 1 (%)*
		Anion Formation	*CO_2 Quench*		
1	5.4	2.0	0.9	91.6	81
2	3.5	2.0	0.9	94.4	
3	5	3.6	1.6	97.2	88
4	4	3.6	1.6	98.2	91
5	4	3.6	1.6	97.8	

After processing some batches on scale, the residence time for the anion formation was adjusted to 3.6 min and CO_2 quench to 1.6 min which gave the highest purity of **1.** Thus, 22 kg of material was processed safely to afford the product using stainless steel tubes and common FMI pumps.

For our process, CO_2 was directly introduced to the reaction stream. Several alternative techniques of introducing gas to the reaction stream have been reported.

Steven Ley (*14*) has reported the use of gas permeable tubing for this type of reaction to deliver gas to a substrate stream in a continuous fashion in a tube-in-tube configuration. His approach, where the substrate stream passes through a Teflon AF-2400 tube, is placed inside another PTFE tube which contains the desired gas under pressure. The gas diffuses into the substrate stream in a safe and controlled manner. This design is useful when reactions are done at ambient temperature. A modelling study about the merits of such gas permeable tubing is discussed by Klavs Jensen (*15*).

Nicholas Leadbeater has reported a variant of the tube-in-tube reactor for the use of carbon monoxide in a palladium-catalyzed alkoxycarbonylation reaction (*16*). Use of carbon monoxide is inconvenient mainly due to the extreme toxicity and poor reactivity of the gas. Nevertheless, carbon monoxide has been traditionally used for carbonylations (*17*) reactions and in most cases these reactions have been done at high pressure and temperature in a batch mode. In the event of an accident, these extreme conditions can lead to disastrous consequences which outweigh the synthetic utility of these reagents. In his report, a design as shown in Figure 4 was adopted. This set up provided access to high pressure and at high temperatures.

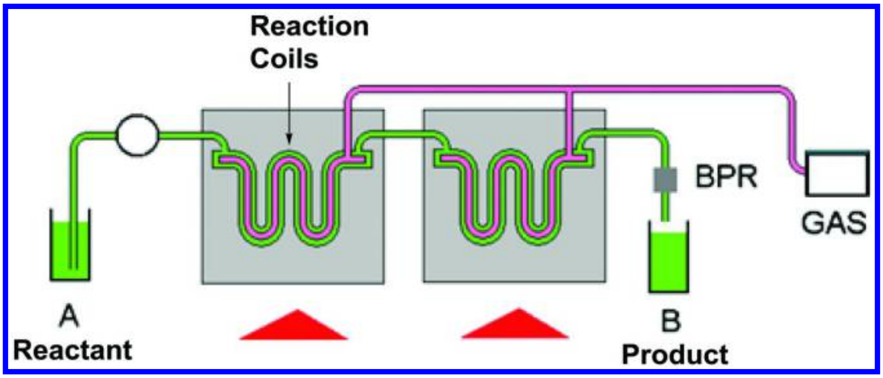


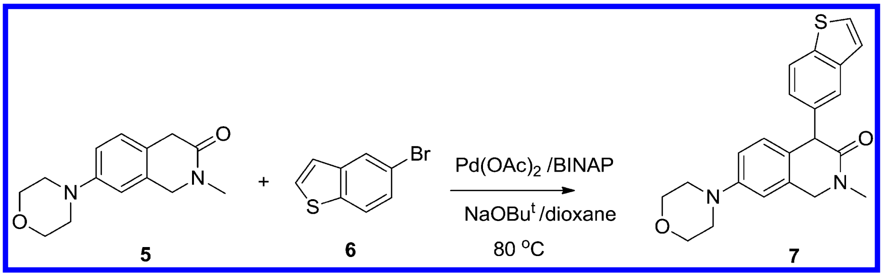
Figure 4. Reactor Configuration

Carbon monoxide was passed through the inner permeable tube and the substrate stream on the outer stainless steel tube in opposite directions. Two back pressure regulators one on the gas inlet and one at the product exit provided the necessary pressure in the lines. Several aryl iodides were converted to their corresponding esters in high yields at 180 psi and 120 °C. This system was further extended to hydrogenations (*18*) of alkenes as well.

Recent advances in continuous flow technologies while harvesting the utility of these reagents offer safer alternatives for large scale production.

Palladium Mediated α-Arylation Reaction Converted to Flow

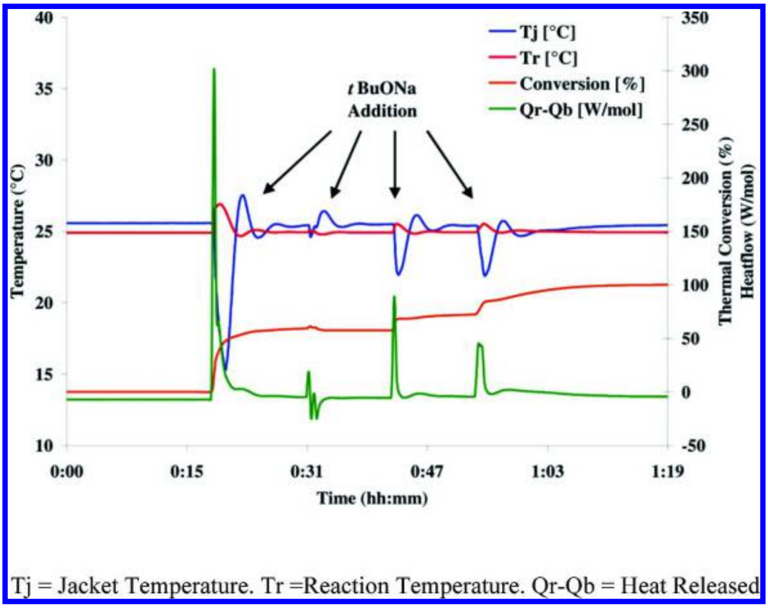
In another AMRI example that was successfully converted from batch to flow, compound **7** (Scheme 3) an intermediate in the synthesis of an API evaluated for the treatment of major depressive disorder, was prepared initially in a batch mode via a palladium-mediated α-arylation process (*19*).



Scheme 3. Palladium-mediated α-arylation reaction

In the batch process, the reactants **5** and **6** and the Pd catalyst were mixed in dioxane followed by the addition of sodium *tert*-butoxide. The mixture was heated to 60 °C until it became self-heating and then the heat source was removed. After the exotherm had subsided, the mixture was then heated to 80 °C until analysis indicated the desired conversion was complete. This reaction was successfully carried out multiple times on 100-300g scale.

Aside from the expected exotherm arising from addition of sodium *tert*-butoxide, no observable exotherm was detected on small scale upon heating to the reaction temperature. Regardless, reaction calorimetry was performed since coupling reactions of this type can potentially be exothermic. The expected exotherm from the sodium *tert*-butoxide addition was rapid and easily controlled by portion wise dosing (Figure 5). The total heat output was mild (−24 kJ/mol, ΔT_{ad} = 7 K), and no significant heat accumulation was observed



Tj = Jacket Temperature. Tr =Reaction Temperature. Qr-Qb = Heat Released

Figure 5. RC1 calorimetry of α-arylation: NaOt-Bu

The thermal profile of the coupling reaction revealed an exothermic event once the system approached approximately 60 °C, at which point the reaction became self-heating (Figure 6). Integration of heat flow indicated that 70% of heat output occurred after the system became self-heating. Total heat output was calculated to be −221 kJ/mol (ΔT_{ad} = 62 K), suggesting that, in the event of a cooling failure, the system would quickly exceed the boiling point of the solvent. An attempt to develop a semi-batch process where one of the reagents (either **5** or **6**) was added portion-wise at high temperature was not successful and resulted in poor quality product.

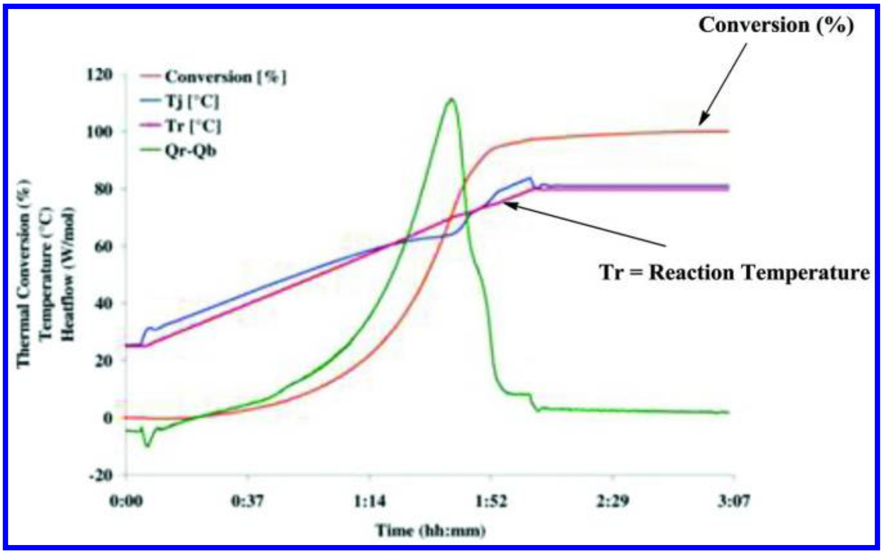


Figure 6. Heat Cycle RC1 calorimetry of α- arylation

Although multiple smaller batches supplied material for our immediate need, a long term solution to this problem was required. The thermal profile clearly pointed out that a batch mode was not possible, hence a continuous flow mode was envisioned. However, one of the limitations of such reactions is the heterogeneous nature of the reaction mixture which severely limits the ability to pump the mixture through the tubing. Particles increase the effective viscosity of the fluid, can clog the pumps, and stop the flow. This is more serious with piston pumps on smaller scale runs compared to peristaltic pumps (*20*) or diaphragm pumps which are less sensitive to clogging.

Design of Flow System

Our initial evaluation considered the nature of the mixture at various temperatures. The approach was to combine all the reagents and heat the mixture to 45 °C, just below the initiation temperature of the reaction, and pass it through a loop made of stainless steel (1/8 inch OD, 10 mL volume) or Hastelloy at 80-90 °C. The reactor design was fairly straightforward with a pump connected to a heated loop and a back pressure regulator set to 10 psi (Figure 7).

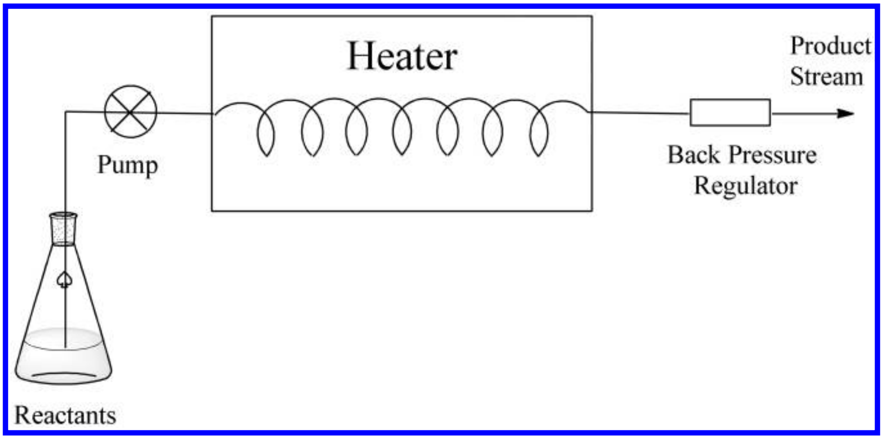


Figure 7. α-Arylation Flow Reactor Design

A mixture of all the reactants in dioxane (*21*) was a slurry until sodium *tert*-butoxide was added. Addition of sodium *tert*-butoxide formed a thin slurry in a 7% dioxane solution which visually dissolved upon heating to 45 °C. However, analysis of this reaction mixture showed ~20% product formation. This meant that the reaction initiated in the pot even before passing through the loop. Reduction of the pot temperature to 30 °C produced ~5% product. Stirring the reagents at 20 °C in dioxane was clearly the best option as no product formed prior to passing through the loop.

An HPLC pump was used for optimization and the reactions were screened at 0.5-1 g scale while varying the residence time and temperature. The product stream was collected and analyzed for reaction conversion (Table 4). The stream was quenched into water, extracted with methylene chloride and concentrated.

Based on the optimization work, it was found that a residence time of 5 min at 90 °C gave the highest conversion and yield. Interstingly, the slurry could be easily pumped through the tubes upon addition of sodium *tert*-butoxide at 20-25 °C without any issues using either an HPLC pump or an FMI piston pump, eliminating one concern of ours. It could be imagined that an identical reactor design with larger tubes sizes could be used to process kilogram quantities of material safely. Further scale up has not yet been considered, however we have modified this batch reaction into what should be an efficient flow system. A simple modification in the set up rendered a safe process.

Table 4. Optimization of the α-Arylation Process

Residence Time (min)	*Temperature (°C)*	*Conversion (HPLC area %)*	*Yield (%)*
5	70	33	18
8	70	55	25
12	70	86	52
5	80	65	36
8	80	88	46
12	80	95	56
5	90	99	74

Conclusions

In conclusion, a two step carboxylation reaction which would have had significant thermal hazards and quality issues on scaling up in a batch mode was converted to a flow mode using stainless steel tubes. Using this set up, 22 kg of material was processed in a regular lab to obtain the product in 88% yield. Similarly, a palladium-mediated α-arylation which posed challenges to scale up in a batch mode was optimized in a flow mode in 74% isolated yield.

Continuous flow chemistry is the next major progression towards safe production of materials that involve hazadrous chemistry. Many interesting methodologies that are routinely used by medicinal chemistry groups are not utilized on large scale due to the inability to develop suitable processes and engineering controls to safely execute them on commerical scale. The benefits of continuous flow chemistry goes beyond a smaller foot print or energy conservation. It opens process chemistry to a new world of those synthetically useful reactions that once were considered unfeasible for large scale production.

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Subject Index