

Safe Scale-Up of Processes Containing Hazardous Species in the Headspace with Inline IR

George Zhou,* Khateeta Emerson, Emily Majusiak, Camille Anderson, and Osama Sudah

Merck & Co., Inc., P.O. Box 2000 RY818-C306, Rahway, New Jersey 07065, United States

ABSTRACT: Inline IR has been applied to evaluate the scale-up of processes that potentially generate hazardous diborane, hydrazoic acid, methyl chloride, or acetylene in the headspace of reactors. In addition, a new, simplified approach to calibrate the online IR analyzer for the measurement of hydrazoic acid in the gas phase has been described.

■ INTRODUCTION

In the pharmaceutical industry, synthetic chemistry has been challenged to make drug substances or their intermediates with high quality in a safe and efficient manner. Several common reaction routes such as borane reduction, tetrazole formation via an azide, deacylation, and alkylation are often used to develop synthetic processes at small scale during the drug discovery phase. However, they involve diborane, hydrazoic acid, methyl chloride, and acetylene, respectively, which pose potential safety hazards especially during process scale-up in the pilot plant and/or factory. The presence of such species, especially diborane and hydrazoic acid, can result in vapor phase explosions even in inert atmospheres. In addition, the headspace concentration in large equipment will be different from that in small vessel at lab due to the difference in liquid to vapor mass transfer. Thus, it is also important to model the large-scale equipment with its mass transfer and purge rates during process scale-up.

Borane reduction is a common reaction widely used in the synthesis of active pharmaceutical ingredients (API) or their intermediates. The presence of diborane in the headspace of a reactor is a safety concern especially during the process scale-up. According to literature,¹ diborane gas is explosive and toxic, and exhibits a broad range of lower explosive limit (LEL). It targets the respiratory system, kidneys, and nerve system. Its LEL is 5000 ppm. Therefore, quantifying diborane levels in the headspace of a reactor is essential for scale-up. Proper inerting of headspace and effective venting are also very important for controlling the process on scale-up.

Thus, to capitalize on the effective but potentially hazardous route, it is important to characterize and quantify the level of such species in the headspace of reactions so that a scale-up strategy can be developed accordingly. Traditional techniques such as GC or GC/MS can be developed to determine the species in the headspace.² However, because of the reactive and hazardous nature, gases such as diborane challenge conventional off-line analytical methods. For example, borane reduction is an effective reaction step used quite often in the synthesis of drug substances. The use of diborane and its derivatives in hydroboration and reduction reactions has been reviewed by Follet on a laboratory and industrial scale.³ With these reactions, a high level of diborane may exist in the headspace of a reactor and may also exceed its LEL. The amount of diborane generated

could constitute a significant percentage of the headspace gases, and it is also unstable offline, rendering analysis undetectable by conventional methods such as GC or MS. A literature search has not resulted in many valuable findings on how to detect its presence and quantify diborane in the headspace of the reactor.

Meanwhile the formation of hydrazoic acid is intrinsic in many chemistry processes that use azides, and it could be formed via acidification of an azide salt such as sodium azide, too. However, hydrazoic acid is extremely toxic and very volatile with a boiling point of 37 °C. The recommended airborne exposure is 0.11 ppm.⁴ Moreover, neat hydrazoic acid or its concentrated solutions are highly shock sensitive.^{5,6} It is explosive when concentration exceeds 100,000 ppm.^{7–10} The pure material has potential to detonate from the energy of a human voice. Thus, reliable vapor-phase measurement of HN₃ is needed to assess the potential vapor-phase hazards of hydrazoic acid in azide reactions especially at scale-up. Furthermore, to improve productivity and efficiency without compromising safety, a systematic approach to map out the risk boundaries of scale-up operation for processes involving hydrazoic acid is highly sought after.

Fortunately there have been several reports^{11–14} to date on the safe scale-up of hazardous reactions including these processes. Caygill et al. illustrated their process development, reaction design, reaction protocols, and a scale-up hazard assessment, based on calorimetry, to both minimize hazards and optimize the way in which reactions are performed.¹¹ Weisenburger et al. reviewed safety issues related to common mistakes and major industrial accidents.¹² They also discussed comprehensive review of process design, scale-down approach to process safety, and explosion and decomposition characteristics of hydrazoic acid. Carrying out a reaction such as azidation at low temperature could be a factor to consider for reaction safety; however, accumulation of high-energy species must be considered. In the diastereoselective introduction of an azido functional group on a functionalized chiral oxazolidinone, Connolly et al.¹⁴ applied in situ FTIR to study the enolization–azidation and observed that accumulation of triisopropylbenzenesulfonyl azide did not occur, resulting in a scale-up process that ran successfully at –40 °C. Another approach is to carry out the hazardous reaction at microscale. By using a

Received: October 3, 2011

Published: December 23, 2011

safe and scalable high-temperature microreactor, Gutmann et al. synthesized 5-substituted tetrazoles from nitriles and hydrazoic acid at unprecedented efficiency.¹³ The in situ generation and secure handling of extremely hazardous HN_3 in a microreactor environment was the key to success and may be suitable for a safe industrial-scale preparation of tetrazole compounds. Because of the potential for slow reactions associated with low temperature and scale-up readiness of microreactors, however, in many cases the project teams have to devote extra effort and time to develop an alternative drug synthesis route to avoid the potential risks associated with running these effective but hazardous reactions at large scale.

While hydrazoic acid might be present for some common processes including tetrazole preparation and other azidations, there are several techniques that can be used to measure hydrazoic acid in the headspace of a reactor. Keicher et al. discussed the safety precautions and practical measures for the safe handling of azides at lab scale.⁵ They describe the analytical techniques and other test methods that allow characterization of the hazardous potential of organic azides qualitatively and quantitatively at an early stage of small-scale preparation. One common method is a UV method to measure the amount of hydrazoic acid captured in a basic receiving container. However, it is indirect and depends on the efficiency of capturing the hydrazoic acid bubbling through the scrubber. More importantly, it is difficult to realize this measurement in real time; as a result, this method cannot provide dynamic data on hydrazoic acid generation in the headspace. Other analytical approaches for hydrazoic acid have been reported by Wiss et al.⁶ During the synthesis of tributyltin azide followed by cycloaddition to prepare a tetrazole ring compound, they applied mid-IR to determine the amount of hydrazoic acid at lab scale. To calibrate the mid-IR, they used 1 N sodium hydroxide to quench the offline headspace sample and then measured the amount of azide anion with UV. With the same calibration methodology, they calibrated and installed a FT-near IR (NIR) analyzer to monitor the hydrazoic acid concentration in the headspace at scale-up. However, the reference UV method involves the bubbling of headspace gas containing hydrazoic acid in a caustic solution in a scrubber. It is time consuming, and its accuracy of measurement might be subject to human error. Thus, a reliable and simple IR method for inline measurement of hydrazoic acid in the headspace of a reactor is advantageous.

In addition, the presence of acetylene gas in the headspace is a major concern, too. Acetylene is very sensitive to excess pressure, excess temperature, static electricity, and/or mechanical shock. It is extremely flammable and readily forms explosive mixtures with air over an unusually broad range of concentration.¹⁵ The explosive limits can range from 2.5 to 100% in air. The high bond energy of the carbon-carbon triple bond makes acetylene explosions more violent than those of most other fuels. For these reasons, the electrical classification of acetylene in the United States is Class 1 Group A.¹⁶ For reference, Group B includes hydrogen and, in some situations, ethylene oxide and butadiene. Due to the special safety controls required for the use of acetylene gas, few, if any, U.S. pharmaceutical pilot plants are rated for Class 1 Group A. In the EU, however, acetylene has an electrical classification of group IIC¹⁷ which also includes hydrogen, and some European pharmaceutical pilot plants are rated for group IIC.

Alkynylation can generate acetylene gas.¹⁸ Although careful control over the release of acetylene gas during the reaction as well as the proper rating of the piping for acetylene emission is

required in all cases, the quantitation of headspace acetylene is also important for process scale-up. Apparently, one can take samples for offline analysis with analytical methods such as GC or GC/MS, but it is challenging to sample and handle acetylene in the headspace of a reactor for offline analysis. In addition, the dynamic information on acetylene generation would be limited. Therefore, it is desirable to use an inline method such as the one using IR to measure the concentration of acetylene generated in the headspace of a reactor and hence to monitor its fate during the entire process.

Finally, methyl chloride (MeCl) or chloromethane exists mostly in the gas phase with a boiling point at $-23.7\text{ }^\circ\text{C}$. MeCl is usually generated as a byproduct in a reaction and Merck's environment limit requires its emission limit to remain $<2\text{ lbs/h}$ (no averaging) which is below the environmental regulation. During the scale-up of a deacylation process that employs hydrochloric acid (reagent) and methanol (solvent), the methyl chloride (MeCl) that is generated as a side product is classified as a Hazardous Air Pollutant (HAP) by US environmental regulations. Therefore, from a process scale-up standpoint, the MeCl generation must be evaluated in the lab to ensure a scale up strategy that allows the MeCl emission rate to remain under the 2 lb/h limit during large scale production. Traditionally, methods used to monitor MeCl gas require that gas passes through a sodium hydroxide or ammonium hydroxide solution with subsequent titration¹⁹ of the scrubber solution. However, this offline approach again lacks dynamic information.

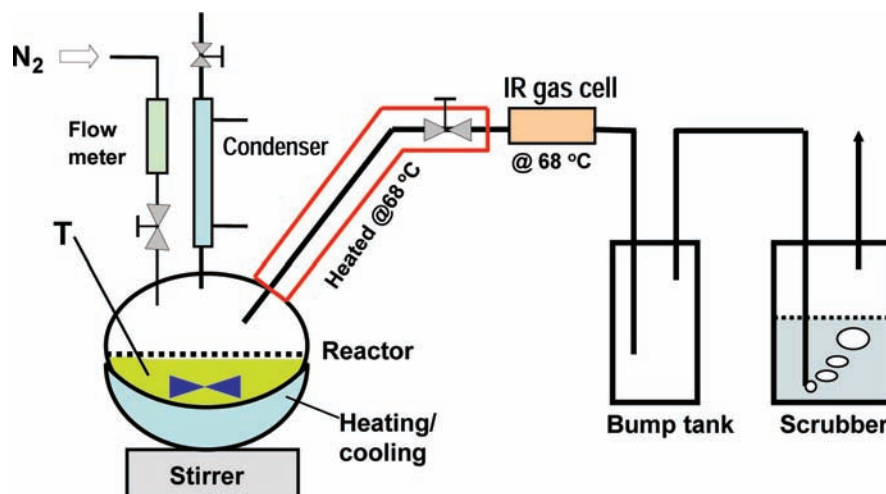
As a result, given the above-mentioned constraints and high demands of process scale-up involving hazardous species, an alternative IR method can be used to study the process by collecting IR spectra of the reaction headspace to measure these species inline in their native format without compromising their chemical integrity. In order to achieve this goal, a special experimental setup which enables the measurement in the headspace, and a methodology that guides the experiment and collects desired headspace spectra are essential. Herein we describe a practical approach for developing the inline IR methods to measure hazardous headspace species including diborane, hydrazoic acid, acetylene, and methyl chloride and subsequently implementing a scale-up strategy that enables these processes to run safely and environmentally friendly.

■ EXPERIMENTAL SECTION

Materials. A diborane standard with 1%(v/v) diborane in nitrogen was purchased from Voltax, Inc., Branchburg, NJ. An acetylene standard containing 99.6% acetylene was obtained from Matheson Trigas Inc., Twinsburg, OH. Several intermediates or APIs of drug candidates made in-house at Merck & Co., Inc. were used in the case studies. They are MK-A for the diborane study in borane reduction, MK-B for hydrazoic acid formation in azidation, MK-C for acetylene generation in alkynylation, and MK-D for methyl chloride byproduct in a deacylation reaction. Solvents such as ethanol (HPLC grade), acetic acid and sodium acetate (both ACS grade), and conventional chemicals (ACS grade) were all obtained from Sigma-Aldrich, St. Louis, MO. Methyl chloride gas (>99.5%) was also purchased from Sigma-Aldrich, St. Louis, MO.

Experimental Setup. The FTIR (ReactIR 4000 by Mettler-Toledo AutoChem, Columbia, MD) with a gas flow-through cell (10 cm path length, ZnSe windows) was used to measure the concentration of hazardous species in the headspace. Scheme 1 shows the inline IR setup. It consists of an inline IR gas cell, a 250-mL reactor, a condenser, a heat controller for heat-tracing the outlet gas line, a magnetic stirrer, a water bath,

Scheme 1. Setup of inline headspace measurement with IR



and a thermometer. Nitrogen purge supply is maintained at 20 mL/min through the headspace of reactor. A scrubber is also required for quenching the potential hazardous species evolved from the reaction. Spectral resolution of 8 cm^{-1} , apodization of Happ-Genzel, spectral region of $4000\text{--}650\text{ cm}^{-1}$, and a DTGS detector were used. Each spectrum is composed of 32 co-added scans. During operation, both IR gas cell and inlet line to the IR gas cell were heated to prevent unwanted condensation of material to be measured. The suggested temperatures for both IR gas cell and inlet line will depend on the dew point of the mixture being studied ($68\text{ }^{\circ}\text{C}$ was used for our studies).

RESULTS AND DISCUSSION

Detection and Quantitation of Diborane–Borane Reduction Scale-Up. The presence of diborane in the headspace of a reactor is indicated in Figure 1, which includes the

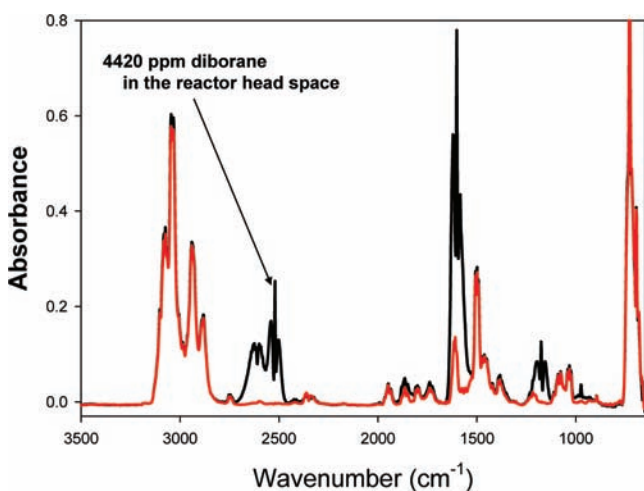


Figure 1. IR vapor-phase spectra of the headspace vapors before (dark line) and after (red line) the addition of a bromoketone. Process starts with borane–THF in toluene.

spectra of vapor phase collected before and after the addition of a reactant, bromoketone, to the solution of borane–THF in toluene. The initial vapor spectrum from the reaction vessel is mostly the same as that of toluene across the entire spectral region since toluene is the solvent. With 4420 ppm diborane in

the headspace, however, there are several regions, unique to diboranes, in the spectrum of a headspace sample taken before the addition of bromoketone. After the addition of bromoketone, borane was consumed via reacting with bromoketone, resulting in the disappearance of diborane in the headspace. Peaks at $2530\text{--}2480\text{ cm}^{-1}$ and $2640\text{--}2570\text{ cm}^{-1}$ are the strong absorption bands, symmetric and asymmetric stretches, of --BH_2 .²⁰ The diborane bridge absorbs very strongly at $1610\text{--}1540\text{ cm}^{-1}$ due to asymmetric, in-phase hydrogen motions. Another band around 1150 cm^{-1} corresponds to the deformation of --BH_2 , and the band at 930 cm^{-1} is the wag of --BH_2 .

The calibration of diborane was built on these diborane peaks with a setup similar to that shown in Scheme 1. In this case one stream of house nitrogen and another of diborane standard with 1% (v/v) diborane in nitrogen were mixed first, then passed through the IR gas cell which was heated at $70\text{ }^{\circ}\text{C}$. Each stream has a mass flow meter to record the flow rate. By varying the flow rates of each stream, different gas mixtures were created, and their corresponding spectra were collected. Figure 2a illustrates that the diborane peak around 2500 cm^{-1} changes in magnitude when its concentration varies from 0 to 1% (v/v). A calibration curve was obtained based on the peak area between 2512 and 2450 cm^{-1} with a baseline defined by 2748 and 2446 cm^{-1} . A linear correlation between the diborane concentration and peak area at 2500 cm^{-1} exists and is illustrated in Figure 2b: $Y = 5.370 \cdot X + 0.067$, where Y is the peak area at 2500 cm^{-1} and X is the concentration of diborane in the gas phase. This calibration curve can be used to quantify diborane concentration in the headspace of a reactor.

As an example, the synthesis of the free base **2** (Scheme 2), an intermediate of a drug candidate MK-A under development at Merck and Co., Inc., involves charging borane–THF into an amide **1** solution in THF at $7\text{--}14\text{ }^{\circ}\text{C}$, followed by heating to $35\text{ }^{\circ}\text{C}$ and maintaining at this temperature for 4 h. Borane-related species, including diborane, could be present in the headspace of the reactor. Scheme 1 shows the experimental setup where an FT-IR analyzer equipped with an online gas flow-through cell was used to monitor the off-gas from the reduction process. The headspace of the reaction vessel was examined continuously by purging dry nitrogen gas through the headspace at a constant flow rate of 20 mL/min.

To quantify the amount of diborane in the vapor phase of the reactor, the above diborane calibration curve was applied and a

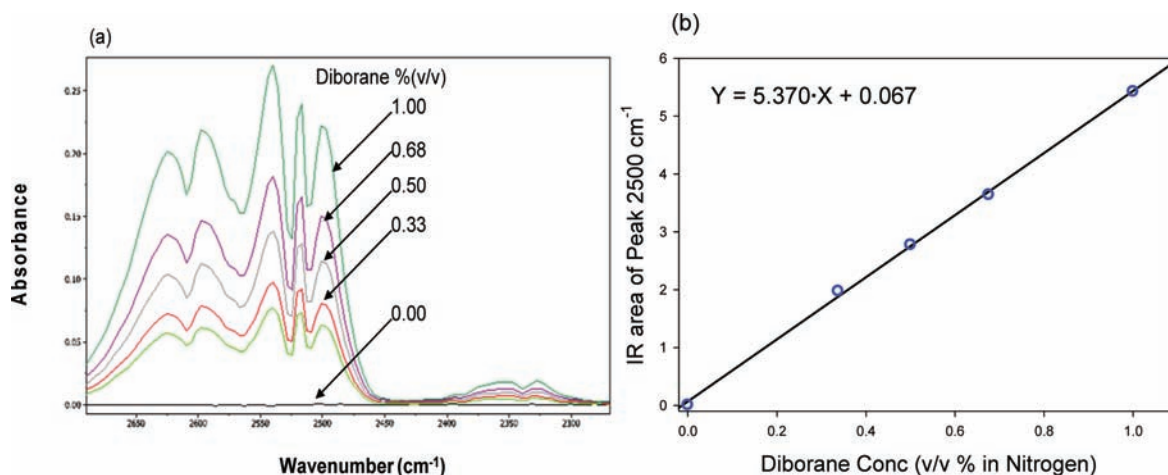
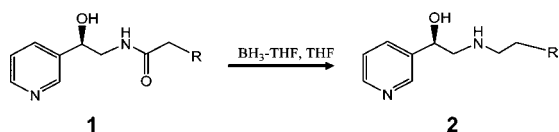


Figure 2. (a) Selected spectra of gases with different levels of diborane and (b) corresponding calibration curve of diborane.

Scheme 2. Reduction with borane–THF to form free base 2 from amide 1



profile of diborane concentration present in the headspace of the reactor was obtained (Figure 3). The top plot in Figure 3

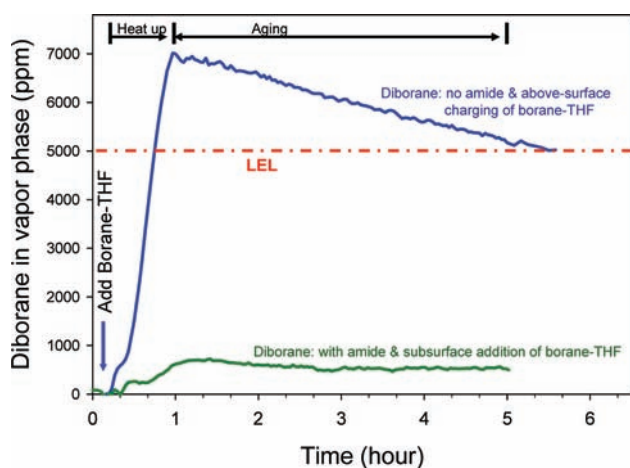


Figure 3. Profiles of diborane in the headspace of free base 2 synthesis under 35 °C with and without the addition of amide 1 by inline vapor-phase IR monitoring.

corresponds to the headspace concentration for the extreme case in which no amide 1 was added to the reactor. This figure indicates a high level (above the LEL) of diborane in the headspace upon heating of the reactor to 35 °C. The diborane concentration peaked near the end of heating step, and then decreased gradually as diborane was removed from the headspace. Concentrations, however, remained above the LEL over four more hours at 35 °C. This diborane level in headspace could occur in reality if the amide 1 substrate was not added or was undercharged, or if borane–THF was added above the liquid surface. Therefore, scale-up is not recommended without a safe plan to address this potential hazard.

When the amide 1 substrate was present and borane–THF was added below the liquid surface, however, the diborane level in the vapor phase decreased by almost 10-fold and remained below 1000 ppm during the entire experiment. The bottom plot in Figure 3 illustrates the profile of diborane in the headspace of such a reaction. This reduction in diborane could be due to the consumption of borane-related active species by the reaction involving the amide 1. Consumption of borane via the amide reaction sufficiently reduces diborane equilibrium concentrations thus minimizing its evolution into the headspace. As a result, considering the limitation of scale-up capability of inline headspace monitoring of gaseous species, a strategy was devised to scale-up this process by subsurface-charging borane–THF, and inline monitoring of the reaction in liquid phase by FT-IR spectrometry, as well as continuously sweeping nitrogen over the headspace of the reactor. As shown in the reaction in Scheme 2, the carbonyl group is consumed upon reaction with borane. Direct inline profiling of the amide carbonyl provides insight into the status of the reaction, and in turn, it allows charging of the reactant in such a manner that the diborane level in headspace would not approach the LEL value. These approaches facilitated reaction scale-up, and consequently, this process was carried out successfully at a pilot plant. Figure 4

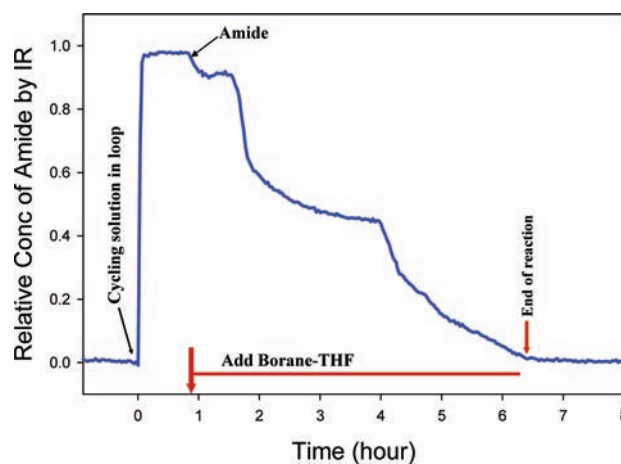


Figure 4. Profile of amide 1 in liquid in the free base 2 synthesis under 35 °C by inline FT-IR monitoring.

illustrates the real-time profile of amide 1 of a scale-up reaction in a 200-gal reactor, which confirms indirectly the smooth

consumption of borane paralleling the rate of addition and a safe scale-up process. In this reaction 10% borane–THF was charged initially around the one hour mark. After pausing ~20 min, addition was resumed. Before the 4-h mark, the emptied borane–THF tank was replaced, and operator shift was also changed. Then the reaction continued with addition of borane–THF until the end of reaction. The inline IR measurement of diborane in the headspace in the lab and amide in the liquid phase at pilot plant provided the information necessary for the process to be scaled up safely with proper engineering control.

Detection and Quantitation of Hydrazoic Acid–Azidation Scale-up. Azides such as sodium azide (NaN_3) and trimethylsilyl azide (TMSN_3) are chemical reagents widely used for the synthesis of triazoles, tetrazoles, and other organic compounds. Recently several synthetic processes, especially those of the intermediates or drug candidates at Merck & Co., Inc., have involved azide chemistry.²¹ As a simple and effective alternative, this work described a special approach by bubbling nitrogen (20 mL/min) through an aqueous solution (~2 mL) containing a small amount (0.1 mmol) of sodium azide (NaN_3) at 50 °C and exiting via the IR gas cell. Upon spiking with 1.0 mL of 5 N hydrochloric acid (>50 equiv), all the azide existed in the form of hydrazoic acid (HN_3) under the strong acidic conditions. Due to the equilibrium of hydrazoic acid between the gas and liquid phases, as HN_3 in the headspace (gas phase) was carried away by N_2 , its level in the liquid phase decreased correspondingly. Over a certain period of time, all the hydrazoic acid passed through the IR gas cell and was measured as illustrated in Figure 5 (the charged NaN_3 was entirely converted to

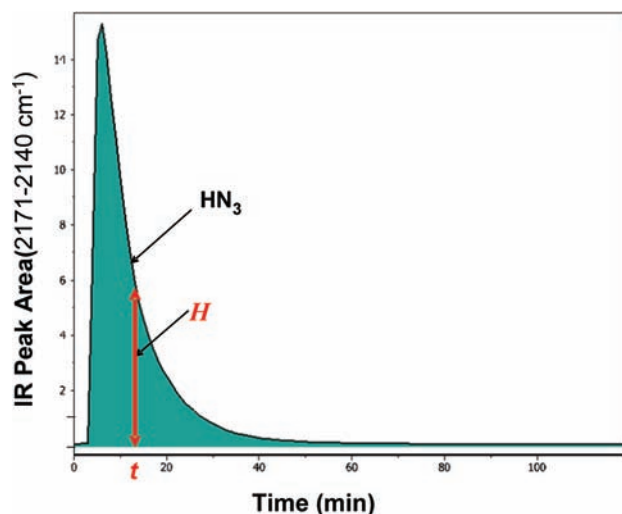


Figure 5. The profile of HN_3 evolution during one of the calibration tests.

HN_3 as determined by external trapping and quantitation). In this way, direct measurement of hydrazoic acid based on the accurate weighing of NaN_3 can be achieved. The peak area was defined as the area of 2171–2140 cm^{-1} with baseline 2187–2059 cm^{-1} . On the basis of the corresponding profile of HN_3 evolution, a calibration factor K was found by:

$$\begin{aligned} K &= [\text{total peak area}] \cdot [\text{flow rate}] / [\text{mg of } \text{HN}_3] \\ &= A \cdot F / M_{\text{total}} \\ &= 595 [\text{area} \cdot \text{mL} / (\text{min} \cdot \text{mg})] \end{aligned}$$

where [total peak area] or A is the total integrated peak profile area (shaded area in Figure 5), [flow rate] or F refers to the flow rate 20 mL/min of N_2 purge (assuming the carrier gas comprises the majority of the gas flow), [mg of HN_3] and M_{total} is the theoretical amount of HN_3 from NaN_3 used in the calibration. The value of 595 [area·mL/(min·mg)] was the average of three calibration replicates.

$$\text{total amount of } \text{HN}_3: M_{\text{total}} = A \cdot F / K \quad (\text{mg})$$

$$\text{for one unit of time: } M_t = H \cdot F / K \quad (\text{mg/min})$$

where M_t is the amount (mg) of HN_3 release in unit time (1 min interval), H is the peak area height per unit time (see Figure 5). Thus, the volume of HN_3 in a unit of time is:

$$\begin{aligned} V_{\text{HN}_3} &= n \cdot R \cdot T / P = M_t \cdot [R \cdot T / (P \cdot M_w)] \\ &= (H \cdot F / K) \cdot [R \cdot T / (P \cdot M_w)] \end{aligned}$$

As a result, the volume ratio:

$$\begin{aligned} V_{\text{HN}_3} / V_{\text{N}_2} &= (H \cdot F / K) \cdot [R \cdot T / (P \cdot M_w)] / F \\ &= H \cdot R \cdot T / (K \cdot P \cdot M_w) \end{aligned}$$

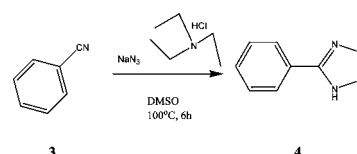
expressed as ppm:

$$\text{ppm (v/v) of } \text{HN}_3 = (H \cdot R \cdot T \cdot 10^6) / (K \cdot P \cdot M_w)$$

where M_w is molecular weight of HN_3 (43), P is 1 atm, T is the temperature under which the measurement was made (K), and R is the general gas constant (0.0821).

To evaluate the factors that affect the formation and evolution of hydrazoic acid in the reactor headspace including acidity, temperature, solvents, and reagents within the common operation ranges, a model reaction (Scheme 3) was used to

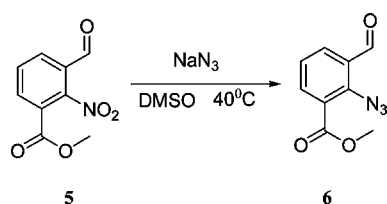
Scheme 3. Formation of 5-phenyl-1H-tetrazole 4 from benzonitrile 3 and sodium azide



study the formation and fate of hydrazoic acid. In this study, reaction temperature was varied from 50 to 100 °C, solvents were varied from DMSO, IPA/water to acetic acid or a mixture of them, pH from 4 to 9, and azide sources from NaN_3 to TMSN_3 . It was found that the pH level of the reaction mixture significantly impacted the amount of hydrazoic acid generated in the headspace since its $\text{p}K_a$ is 4.7. In a protic solvent, a high level of hydrazoic acid (>48,000 ppm) was observed when running reactions with pH below or near 4.7. When the pH is higher than 7, the amount of HN_3 in the headspace is relatively low. In addition, TMSN_3 is also found to be as effective as NaN_3 as the source of azide when generating hydrazoic acid in the headspace of a reaction.

In the synthesis of methylazido formylbenzoate 6, an intermediate of drug candidate MK-B at Merck & Co., Inc., nitroaldehyde 5 is reacted with NaN_3 in DMSO (Scheme 4). To evaluate the potential hazards associated with HN_3 for process scale-up, inline FTIR has been applied to measure the formation of hydrazoic acid in the headspace as illustrated in Scheme 1.

Scheme 4. Formation of methylazido formylbenzoate 6 from nitroaldehyde 5 and sodium azide



In this case nitroaldehyde 5 (2.0 g, 9.56 mmol) and sodium azide in DMSO (10 mL) were stirred at 40 °C.

The presence of hydrazoic acid was observed in the headspace of the reaction vessel during the reaction at 40 °C (Figures 6 and 7). It reached a maximum (max: 3180 ppm) within 30 min. As the reaction continued, the HN_3 level went down, and it was eventually depleted as nitrogen gas slowly carried it away via the scrubber. While this level is below detonation threshold, we wanted to evaluate the possibility to further lower the amount of hydrazoic acid liberated. The most obvious way to achieve this goal was to buffer the reaction media by raising the pH in protic solution to reduce the likelihood of forming and potentially vaporizing hydrazoic acid. As a result, triethyl amine (TEA) was added to this process. In the modified reaction, nitroaldehyde 5 (2 g) in DMSO (10 mL) was charged with TEA (194 mg), heated to 40 °C and charged with NaN_3 (684 mg), and then aged at 40 °C for 2–3 h. With the addition of TEA, the pH of the media increased to 8, and there was no noticeable amount of HN_3 formed in the headspace when using 20 mol % of TEA. Therefore, the reaction was successfully scaled up by using 20 mol % of TEA to avoid any formation of HN_3 in the headspace in addition to adopting the proper engineering control such as applying a continuous N_2 sweep over the reactor.

Detection and Quantitation of Acetylene–Alkynylation Scale-Up. Although careful control over the release of acetylene gas during the alkynylation reaction is required in all cases, the quantitation of headspace acetylene would be beneficial to determining where this chemistry could be performed on kilogram scale. That is, it becomes necessary to investigate if acetylene is generated and at what concentrations it exists in the headspace of a reactor during process scale-up.

First, the inline IR analyzer (Scheme 1) was calibrated by passing through the IR flow-through cell gas mixtures composed of different amounts of nitrogen gas and the acetylene standard. When the gas mixture passed through the IR gas cell,

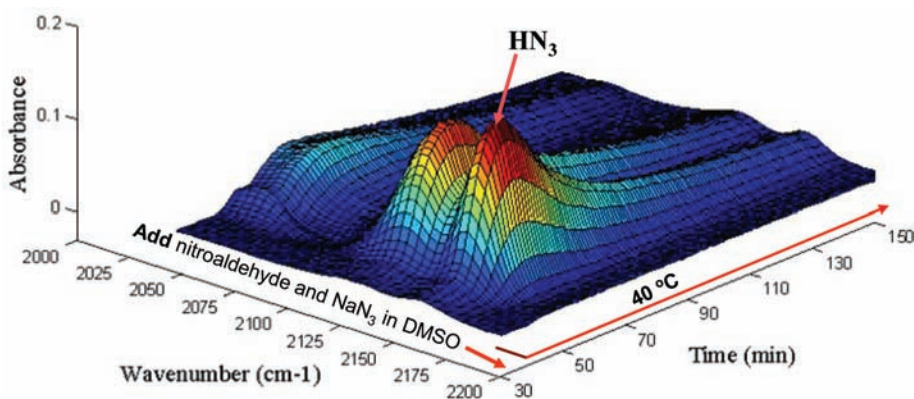


Figure 6. Three dimensional (3D) reaction spectra of gases exiting the headspace of a reaction: nitroaldehyde 5 (2 g) in DMSO (10 mL) is heated to 40 °C and charged with NaN_3 (684 mg).

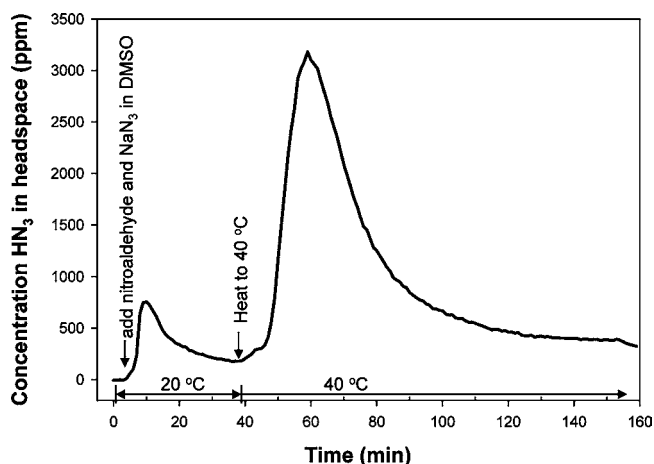


Figure 7. Corresponding profile of hydrazoic acid (HN_3) of reaction illustrated in Figure 6.

the corresponding spectra were collected. Figure 8a illustrates that the 3260 cm^{-1} peak of acetylene changes when its concentration varies from 0 to 1% (v/v). On the basis of this peak area, defined by the area between 3281 and 3236 cm^{-1} with the two-point baseline (3400 and 3175 cm^{-1}), a calibration curve was obtained, $Y = 3.6611 \cdot X + 0.1544$, where Y is the peak area at 3260 cm^{-1} and X is the concentration of acetylene % (v/v) in the gas phase measured (Figure 8b). Clearly, a linear correlation between the acetylene concentrations and the peak area at 3260 cm^{-1} exists. Thus, the profile of acetylene in the reactor headspace can be obtained by converting the peak area to concentration, $[\text{acetylene}] = (H - 0.1544)/3.6611\%$ (v/v), where H is the unit peak area for a unit time (1 min interval).

Second, as an example, in the preparation¹⁸ of alkyne cyclopropanol 9 (Scheme 5), an intermediate of drug candidate MK-C at Merck & Co., Inc., the cyclopropanol 7 is deprotonated with hexyllithium in THF. It is then charged to a solution of the Li acetylide ethylenediamine complex 8 in N,N' -dimethylpropyleneurea (DMPU). After aging at 52 °C for 2–3 h, the reaction was quenched with aqueous HCl. Then, after an aqueous workup, it was concentrated to form the alkyne cyclopropanol 9. Even though much effort has been devoted to selecting the proper solvents and using a sacrificial base to minimize the evolution of acetylene gas, the potential to form acetylene gas in the headspace from the decomposition of 8 was a major safety concern for this process and warranted further investigation.

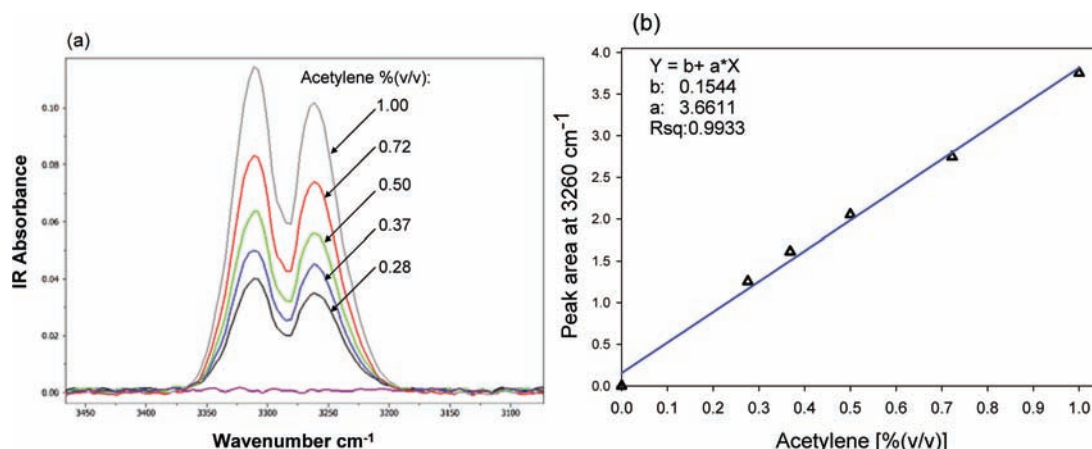
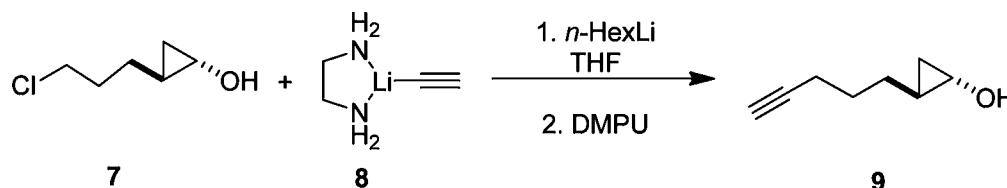


Figure 8. (a) Selected IR spectra of gases with different levels of acetylene around peak 3260 cm^{-1} and (b) corresponding calibration curve for acetylene.

Scheme 5. Optimized conditions for formation of 9



In order to understand and quantify the amount of acetylene produced during this reaction, an IR analyzer was used to measure the evolution of acetylene gas (absorption at 3260 cm^{-1}) in the headspace. The gas phase in the reactor was examined over the entire course of the reaction by purging dry nitrogen gas through the headspace at a rate of 20 mL/min . A condenser at $5\text{ }^{\circ}\text{C}$ was used to minimize the loss of THF.

When the optimized procedure using a sacrificial base and 1.1 equiv of **8** was performed in the apparatus equipped with the IR analyzer, it was observed that acetylene was still evolved during the reaction (Figure 9), with the majority of the acetylene

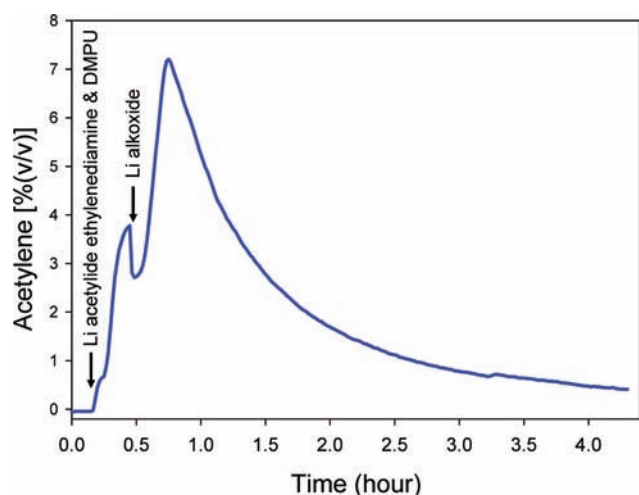


Figure 9. Acetylene profile during the formation of alkyne cyclopropanol **9** from cyclopropanol **7** and Li acetylide ethylenediamine complex **8**.

evolved during the early stage of the reaction. It was also found that suspending **8** in dry DMPU led to some acetylene release

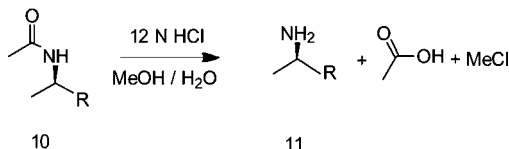
(<1% acetylene in the headspace). During the reaction, the bulk of acetylene was released upon the addition of lithium alkoxide solution of **7** in THF to the suspension of **8** in DMPU and the subsequent heating to $50\text{ }^{\circ}\text{C}$. At its highest point, the level of acetylene estimated in the headspace during the reaction was 7.2% (Figure 9). The acetylene level reached this point at 50 min and then slowly dropped over the remainder of the reaction due to the continuous purge of nitrogen gas through the headspace. Monitoring was continued during the quench of the reaction with 1 M HCl, but no acetylene release was noticed at this point. Because of the relatively high level of acetylene which can potentially be produced by this reaction, care should be taken when using **8** on any scale to avoid potentially dangerous explosions from the buildup of acetylene.

Finally, due to the exothermic behavior of the reaction mixture, the reaction should be slowly heated to $50\text{ }^{\circ}\text{C}$ to avoid mild exotherms that begin at $50\text{ }^{\circ}\text{C}$. Adequate and proper venting should be provided for potential acetylene gas generation. While using reflux condenser to minimize the loss of solvent such as THF, an appropriate level of N_2 sweep must be used on the vessel during the heating up to $50\text{ }^{\circ}\text{C}$ and subsequent aging so that the acetylene in the headspace can be controlled to a low level. Meanwhile, the aqueous waste should not be drummed and sealed immediately. It is recommended that the aqueous cuts be combined in a vessel and aged at $35\text{ }^{\circ}\text{C}$ with a N_2 sweep for a few hours prior to drumming. On the basis of these results, safely performing this chemistry on kilogram scale was permitted. As a result, with all the precautions mentioned above, applying adequate nitrogen sweep to maintain low levels of acetylene in the headspace, slowly heating to and aging at $50\text{ }^{\circ}\text{C}$, and using efficient cooling in the reflux condenser to minimize the loss of solvent, the reaction was scaled up successfully at kilo lab scale.

Detection and Quantitation of Methyl Chloride–Deacylation Scale-Up. In a deacylation process, a synthetic process to make an intermediate of a drug substance MK-D at

Merck & Co., Inc., the reaction starts with *R*-acetamide **10** involving concentrated hydrochloric acid (HCl) and methanol (MeOH) in water (Scheme 6). Due to its volatile

Scheme 6. Deacylation process with *R*-acetamide **10 to form *R*-amine **11** in hydrochloric acid and methanol in water**



nature, MeCl could be formed but is hard to be directly detected during the reaction by conventional offline analyses without trapping. Its presence could be detected by ^1H NMR analysis of reaction solutions after trapping it with an amine at the end of a reaction. To map out a timely strategy for safe operation while adhering to environmental limits at scale, it is necessary to evaluate the risk associated with the procedure with regard to the formation and fate of MeCl.

Initially, the inline IR with the gas-flow-through cell was calibrated with standard methyl chloride gas.

By mixing different amounts of nitrogen gas with a MeCl standard, the calibration was obtained in Figure 10. The gas

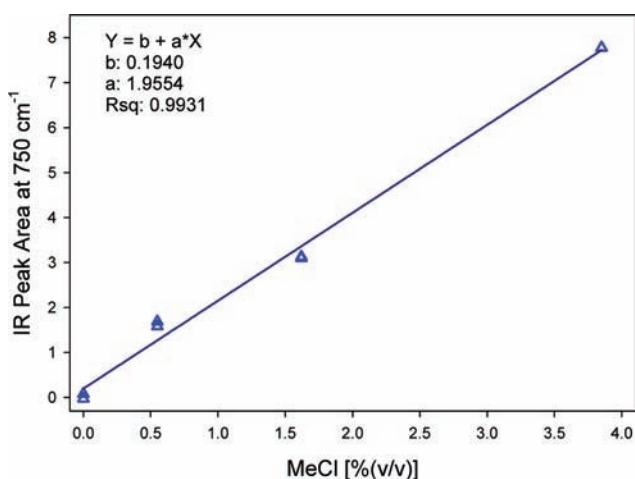


Figure 10. Calibration curve of MeCl in nitrogen gas with inline IR.

mixture was passed through the IR gas cell while collecting corresponding spectra of headspace. Figure 11 illustrates that the 750 cm^{-1} peak of MeCl changes during the reaction. On the basis of this peak area, defined by the area between 753 and 738 cm^{-1} with a single-point baseline at 786 cm^{-1} , a calibration curve of MeCl was obtained: $Y = 1.9554 \cdot X + 0.1940$.

The lab process was carried out in the lab on the setup illustrated in Scheme 1. The reaction was started with 5.94 g of *R*-acetamide **10** (16.98 mmol), 14.9 g of water, and 17.6 g of concentrated HCl (178.4 mmol), and a gas flow rate of 60 mL/min (total flow is assumed to be the same as the N_2 sweep). The system was vented to a scrubbing solution (4 M NaOH). Results of this reaction for the gas-phase study on MeCl evolution are illustrated in Figure 11 as the selected reaction spectra and in Figure 12 as the corresponding profile of MeCl release obtained

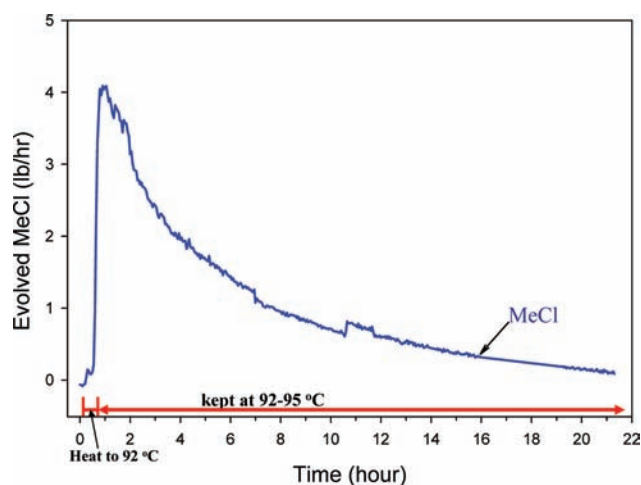


Figure 12. Evolution profile of MeCl during the deacylation of *R*-acetamide **10**, normalized to the scale of 27-kg *R*-acetamide **10**.

with inline IR monitoring. The profile of MeCl in Figure 12 has been normalized to the scale of 27-kg *R*-acetamide **10**. It confirms that MeCl formed significantly during the reaction. In this run the total amount of MeCl generated and integrated via the N_2 purge is about 24% of the total HCl. Figure 12 also illustrates that 0.81 mol/min (41 g/min) or >4 lb/h MeCl will be generated at the peak, which means that venting would exceed the

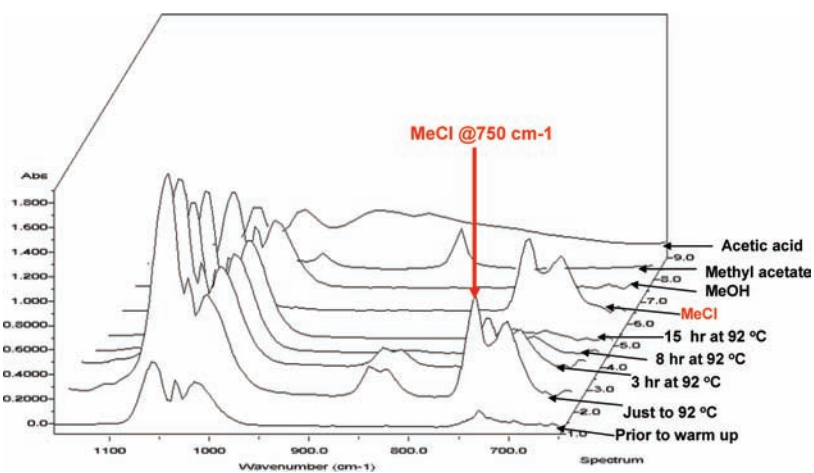


Figure 11. Selected FTIR vapor spectra during the deacylation of *R*-acetamide **10**, illustrated together with several pure chemicals in $1150\text{--}650 \text{ cm}^{-1}$.

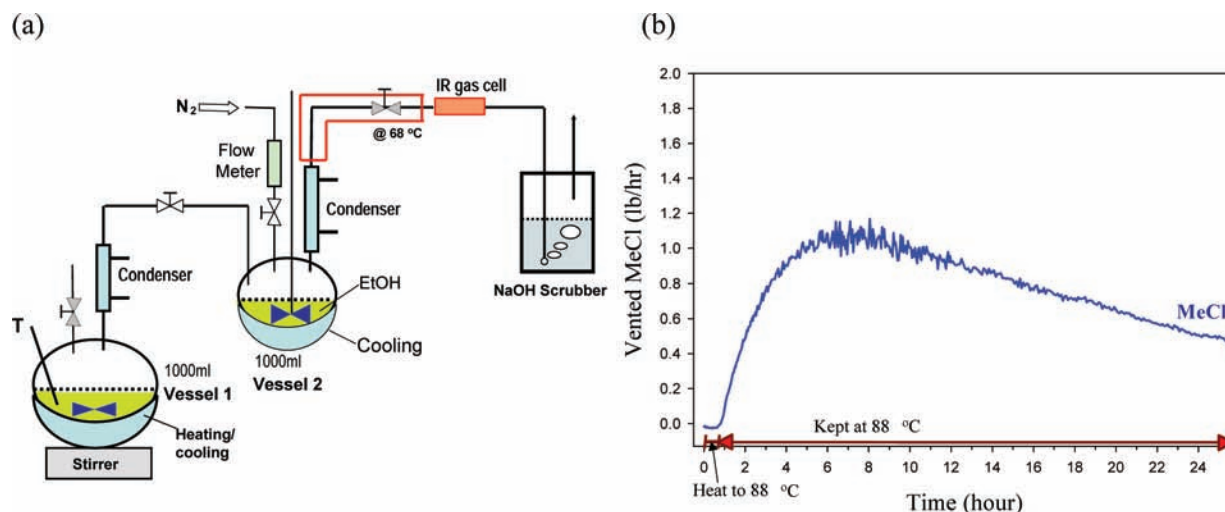


Figure 13. (a) Simulated setup for scale-up and (b) the profile of MeCl at 750 cm^{-1} evolved during the deacylation of *R*-acetamide **10**, normalized to the scale of 27-kg *R*-acetamide **10**.

state limits. MeCl needs to be scrubbed before releasing or burned with an incinerator.

A strategy for a compliant scale-up is needed while adhering to environmental regulations in the pilot plant. Because of the potential high evolution of MeCl during the scale-up, $>4\text{ lb/h}$ MeCl at the peak, an effective scrubber has to be incorporated in the process. Because there is significant solubility of MeCl in EtOH at $0\text{ }^{\circ}\text{C}$ (about 1.5 M at room temperature and higher at $0\text{ }^{\circ}\text{C}$), the EtOH scrubber can minimize the evolution rate of MeCl to below the limit for emissions. Figure 13a shows such a design where a 60-g (*R*-acetamide **10**) scale reaction takes place in vessel 1 at $88\text{ }^{\circ}\text{C}$ with a $0\text{ }^{\circ}\text{C}$ condenser. Meanwhile, the vent to a catch tank lies below the surface, and the temperatures of both the ethanol catch tank (vessel 2) and its condenser were set at $0\text{ }^{\circ}\text{C}$. At the end of the experiment, a mass balance on the Cl⁻ species was conducted by measuring the concentration of HCl in the end-of-reaction solution, determining the concentration of MeCl in the ethanol in vessel 2, and finding the amount of MeCl that escaped from vessel 2 through integration of the headspace FTIR data collected between vessel 2 and the NaOH bubbler. The end-of-reaction solution had 55% of the initial HCl charged, the ethanol in vessel 2 had MeCl at 7% of the initial HCl charge, and the FTIR detected MeCl at 23% of the initial HCl charge. Overall, a reasonable Cl⁻ mass balance was achieved at 85% where 15% of the Cl⁻ that was unaccounted for was likely due to the uncertainties associated with sampling the ethanol in vessel 2 and the offline GC analysis.¹⁹

The MeCl profile (FTIR data) from the above 60-g *R*-acetamide **10** reaction was normalized to the scale of 27-kg *R*-acetamide **10** batch and illustrated in Figure 13b. The data indicated that the use of cold ethanol in vessel 2 reduced the peak emission of MeCl to 1.2 lb/h which satisfied the emission limit of 2 lb/h. On the basis of these results, a process setup at pilot plant essentially identical to that shown in Figure 13 but without a nitrogen sweep was used to execute the 27-kg *R*-acetamide **10** reaction. The ethanol vessel 2 in the pilot plant was well mixed, and its subsurface insertion line was substantially submerged in ethanol and fed the reaction emission from vessel 1 right to the tip of the agitator, allowing enhanced MeCl capture (much more effective bubble dispersion and longer residence time versus those in the lab runs). As a result, the MeCl capture vessel 2 at the pilot plant performed better

than what was achieved in the lab since, in the pilot plant, 40% of the initial HCl charge was captured in vessel 2 as MeCl (versus 7% in the lab). This is another example where inline headspace IR measurement has been successful in obtaining kinetic information on the formation of chemical entities. In this case, the headspace IR data enabled a safe and timely scale-up of chemistry in the pilot plant while adhering to environmental regulations.

CONCLUSION

A method of using an inline IR analyzer to measure the hazardous species diborane, hydrazoic acid, acetylene, and methyl chloride in the headspace of reactions has been described. In addition, a new approach has been developed for calibration of the inline IR analyzer for measurement of hydrazoic acid, given the reactive nature of hydrazoic acid and unavailability of a reference standard. The development and application of these inline IR methods have made significant improvements for safety and eliminated the need for sampling headspace gas containing hazardous species for offline measurements. With the inline measurement of hazardous species in the headspace, dynamic process information has been obtained for use in optimizing processes including borane reduction, azidation, alkynylation, and deacylation. Most importantly, subsequent scale-up strategies that are safe and environmentally friendly have been developed and implemented.

AUTHOR INFORMATION

Corresponding Author

george_zhou@merck.com

ACKNOWLEDGMENTS

We gratefully appreciate Dr. Thientu Lam in the initial development of this work. We thank Paul Fernandez, Claire Lee, Yong Liu, Joe Kukura, Mike Ward, Tseng-En Hu, and Mahmoud Kaba for their cooperation and helpful discussions in this work. We also are grateful for valuable scientific input from Ephraim Bassan.

■ REFERENCES

- (1) Ullmann, F. *Ullmann's Encyclopedia of Industrial Chemistry*, 6th ed.; Wiley-VCH: Weinheim, 1999; Vol. 3, p2336.
- (2) Dryahina, K.; Pehal, F.; Smith, D.; Španel, P. *Int. J. Mass Spectrom.* **2009**, *286*, 1.
- (3) Follet, M. *Chemistry and Industry*; Society of Chemical Industry: London, United Kingdom, 1986; Vol. 4, pp 123–128.
- (4) *International Chemical Safety Cards*, No. 0950; Azide, Recommended Exposure Limits (REL); NIOSH (National Institute for Occupational Safety and Health), 1997.
- (5) Keicher, T.; Loebbecke, S. Lab-scale synthesis of azido compounds: safety measures and analysis. In *Organic Azides*; Braese, S.; Banert, K., Ed.; John Wiley & Sons Ltd.: Chichester, UK, 2010; pp 3–27.
- (6) Wiss, J.; Fleury, C.; Onken, U. *Org. Process Res. Dev.* **2006**, *10*, 349–353.
- (7) Brase, S *Angew. Chem., Int. Ed.* **2005**, *44*, 5188.
- (8) *Ullmann's Encyclopedia of Industrial Chemistry*; VCH Verlag: Weinheim, 1989; Vol. A13, pp 193–197.
- (9) Rozenberg, A. S.; Arsen'ev, Y.; Voronkov, V. G. *Combust. Explos. Shock Waves (Engl. Transl.)* **1973**, 271–277.
- (10) Pannetier, G.; Lecamp, M. M. *Présentés Soc. Chim.* **1954**, 1068–1070.
- (11) Caygill, G. B. *Chem. New Zealand* **2003**, *67*, 66–68.
- (12) Weisenburger, G. A.; Vogt, P. F. *Org. Process Res. Dev.* **2007**, *11*, 1087–1090.
- (13) Gutmann, B.; Roduit, J.; Roberge, D.; Kappe, C. O. *Angew. Chem., Int. Ed.* **2010**, *49*, 7101–7105 S7101/1–S7101/12.
- (14) Connolly, T. J.; Hansen, E. C.; MacEwan, M. F. *Org. Process Res. Dev.* **2010**, *14* (2), 466–469.
- (15) Pässler, P.; Hefner, W.; Buckl, K.; Meinass, H.; Meiswinkel, A.; Wernicke, H.-J.; Ebersberg, G.; Müller, R.; Bässler, J.; Behringer, H.; Mayer, D. Acetylene. In *Ullmann's Encyclopedia of Industrial Chemistry*; Wiley-VCH: Weinheim, 2008.
- (16) Special Hazards of Acetylene. <http://www.msha.gov/alerts/hazardsofacetylene.htm>.
- (17) Health Protection Agency. http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1246260034064.
- (18) Bassan, E. M.; Baxter, C. A.; Beutner, G. L.; Emerson, K. M.; Fleitz, F. J.; Johnson, S.; Keen, S.; Kim, M. M.; Kuethe, J. T.; Leonard, W. R.; Mullens, P. R.; Muzzio, D. J.; Roberge, C.; Yasuda, N. *Org. Process Res. Dev.* **2011**, DOI: 10.1021/op2002497.
- (19) Method 1001: Methyl chloride. *NIOSH Manual of Analytical Methods*, 4th ed.; U.S. Department of Health and Human Services, Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health: Cincinnati, OH, 1994
- (20) Colthup, N. B. *Introduction to Infrared and Raman Spectroscopy*, 3rd ed.; Academic Press: San Diego, CA, 1990; Chapter 12, pp 355–357.
- (21) Chen, C.; Frey, L. F.; Shultz, S.; Wallace, D. J.; Marcantonio, K.; Payack, J. F.; Vazquez, E.; Springfield, S. A.; Zhou, G.; Liu, P.; Kieczkowski, G. R.; Chen, A. M.; Phenix, B. D.; Singh, U.; Strine, J.; Izzo, B.; Krska, S. *Org. Process Res. Dev.* **2007**, *11*, 616–623.