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COMMUNICATION

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The Safe Use of Sodium Hydride on Scale: The Process Development of a Chloropyrimidine Displacement

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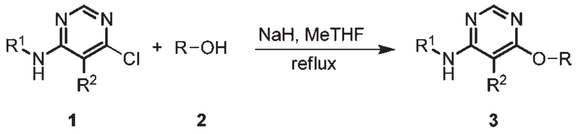
Supporting Information

ABSTRACT: Sodium hydride was found to be the best base for a displacement reaction on a chloropyrimidine. Due to the insolubility of sodium hydride in all solvents and high reactivity with atmospheric moisture, solutions dealing with the associated safety concerns on kilogram scale are described. The use of sodium hydride in premeasured dissolvable bag packaging (SecuBags), online process analytical technology (PAT) to monitor the hydrogen off-gas, and the development of analytical methods to monitor residual polymer and potential degradation products allowed for a successful scale-up and on-time delivery of a quality product.

INTRODUCTION

We recently required kilogram quantities of pyrimidine **3** starting from chloropyrimidine **1** and alcohol **2** (Scheme 1). The initial conditions provided to the process research group by the medicinal chemistry group were the use of 3.2 equiv of sodium hydride (NaH) in refluxing tetrahydrofuran (THF) for 24 h. Our first objective for the process development of this step was to avoid the use of NaH. While some of our industry counterparts have demonstrated the use of sodium hydride on scale, we historically had avoided the use of NaH on kilogram scale due to its inherent safety concerns: insolubility in all solvents and high reactivity to atmospheric moisture.[1,2] For this reason, alternative bases such as NaHMDS, BuLi, hexylLi, *t*-BuOK, *t*-BuONa, Cs_2CO_3, and CsOH were screened. Unfortunately, these bases afforded low yields and unacceptable impurity profiles. Because of an extremely tight delivery timeline, we chose to use NaH in our first campaign. Since sodium hydride is insoluble in all solvents and highly reactive to moisture, we initiated the development of a protocol for the use of NaH on scale. Three main areas needed to be addressed. (1) The physical handling of the sodium hydride from the time it enters the reactor until it is quenched, (2) controlling the release of H_2 during both the deprotonation and quenching of the reaction, and (3) assurance of a complete quench of excess NaH prior to continuing the process.

Scheme 1. Reaction of chloropyrimidine 1 with alcohol 2 to provide pyrimidine 3 using sodium hyrdride as the base



SAFE HANDLING OF SODIUM HYDRIDE

Equipment Setup. A flush bottom drain valve reactor was chosen to prevent collection of solid NaH at the base of the reactor. Dedicated cleaned and solvent-rinsed pumps and lines were used for all transfers. A pressure check of the reactor and the shell side of the process condenser ensured no leaks were present in the condenser coil. As an added precaution, the reflux condenser was set to 'distill' mode to avoid 'wash back' to the batch during the reaction. The reactor was dried and freed from reactive solvents by refluxing with 2-methyl tetrahydrofuran (MeTHF). The reactor contents were rigorously tested for water content by KF and for residual methanol and acetone by GC prior to addition of NaH to the reactor.[3] Lastly, a policy was established that the suspension of NaH would not be transferred into or out of the reactor prior to quenching with the exception of reaction monitoring;[4] this ensured that the pumps and lines would not become contaminated with sodium hydride.

Charging of Sodium Hydride. Solid NaH is typically packaged as a 60% dispersion in mineral oil to minimize the risk of exposure to atmospheric moisture as well as improved handling by decreasing the dusty nature of the dry power. Solid NaH will

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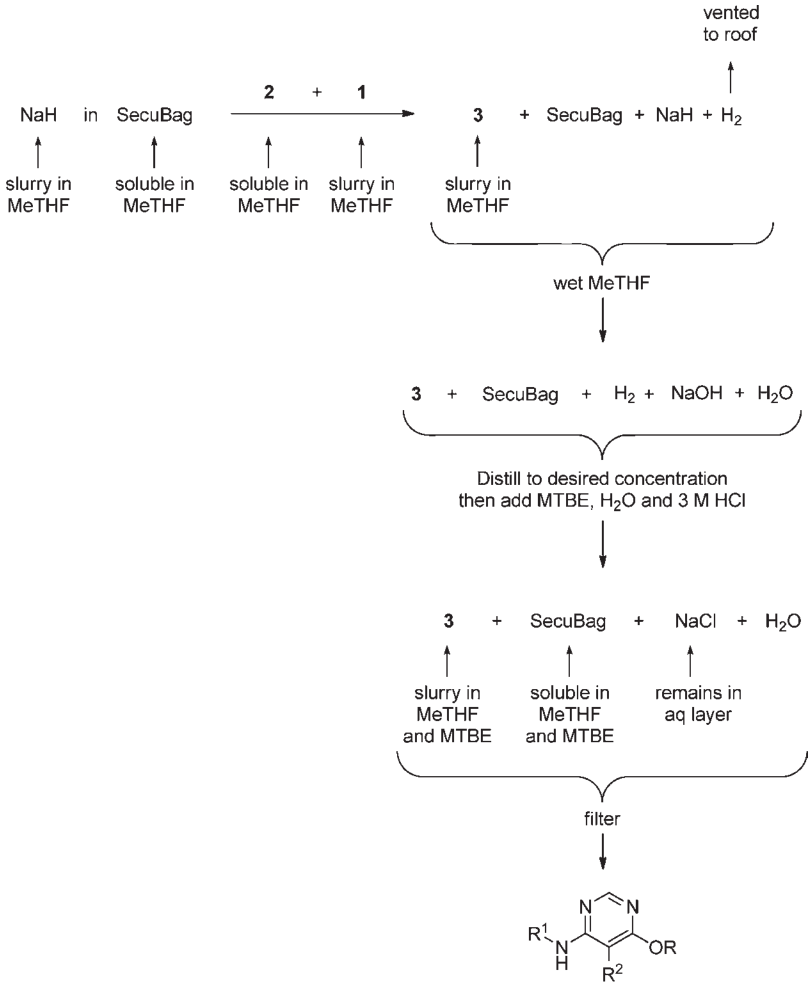
Scheme 2. Depiction of developed reaction process



produce about 1 L of H_2 gas per gram of NaH in the presence of a proton source. In addition, the associated exotherm provides sufficient heat to ignite the evolved H_2 gas. The risk of ignition during the addition of NaH to the reactor was eliminated by using NaH in dissolvable bag packaging (SecuBags) from Chemetall Foote Corp.[5,6] The risks associated with waste disposal of unused NaH were also eliminated since the bags were purchased in premeasured quantities; the entire bag was used in the reaction.

Reaction Process Design and Hydrogen Release during the Deprotonation Stage. Our attention now turned to the design of the reaction process. When designing our process, we needed to incorporate the SecuBags into the reaction and control the release of H_2 during the deprotonation stage. SecuBags are completely soluble in cyclohexane, toluene, *tert*-butylmethylether (MTBE), THF, MeTHF, and dimethylacetamide.[7] Experimentally, our solvent choice was also restricted by the limited solubility of the chloropyrimidine **1**. We determined that THF and MeTHF were the best solvents for the displacement reaction, and ultimately we chose MeTHF due to its higher boiling point and 'greener' properties. In MeTHF at 80 °C the reaction was complete in less than 15 h vs 24 h when THF was used. The developed reaction process is depicted in Scheme 2.

Operationally, the NaH-containing SecuBags were charged to the empty reactor *via* the manhole. The reactor was purged of air by first pressurizing the reactor with nitrogen and then venting the vessel. This cycle was repeated five times. For the remainder of processing, a nitrogen sweep was applied using a set flow of nitrogen. Vacuum was not applied to eliminate the risk of the SecuBags bursting under negative pressure. The MeTHF was added, and agitation started after 10 min. The SecuBags immediately dissolved upon addition of MeTHF to give an indicative gray suspension. This suspension was heated to 80 °C, and a solution of alcohol **2** in MeTHF was added dropwise, followed by a suspension of chloropyrimidine **1** in MeTHF. The deprotonation of starting materials **1** and **2** at 80 °C was instantaneous; this limited the accumulation of the proton source and ensured that the rate of H_2 release was directly controlled by the rate of the addition of each intermediate. The H_2 released during the deprotonation was diluted with nitrogen and vented.

■ QUENCH

Having developed a safe protocol to deprotonate the starting materials, our focus turned towards how to safely quench the excess sodium hydride upon reaction completion. The process utilized 3.2 equiv of NaH even though experimentally, >2.4 equiv

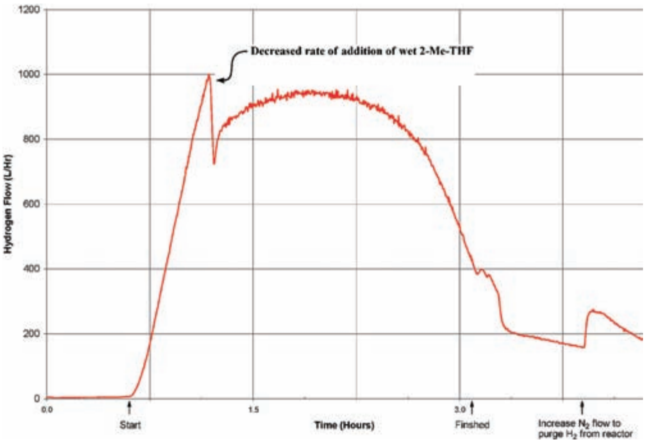


Figure 1. Graphical plot of hydrogen off-gassing during the quench of excess NaH. Start = the start time of wet MeTHF addition; Finished = the time that the wet MeTHF addition finished.

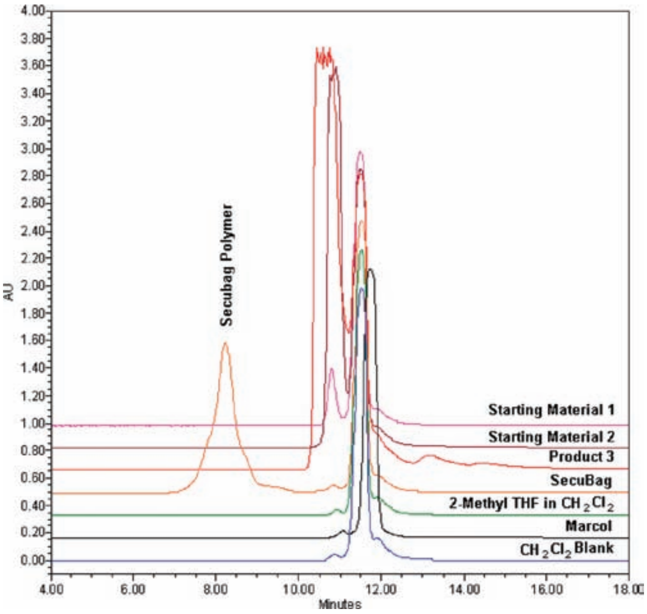


Figure 2. Size exclusion chromatograph with UV detection at 215 nm.

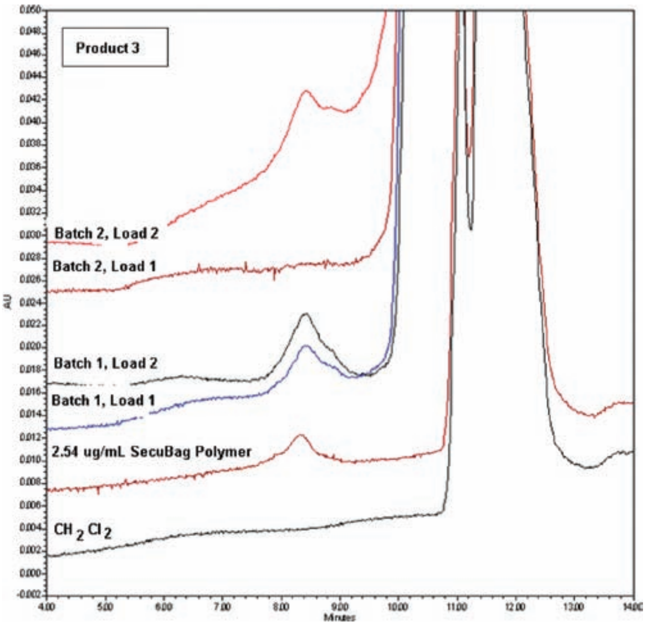


Figure 3. Analysis of batch samples of product **3** using size exclusion column to measure residual SecuBags.

was required for complete consumption of starting material.[8] We used 3.2 equiv because we did not split open the SecuBags containing NaH. As 2 equiv of NaH is consumed during the deprotonation of starting materials **1** and **2**, 1.2 equiv of active NaH remained to be quenched. Typically, the remaining equivalents would be quenched at ambient temperature with isopropanol. This would provide a safe, slow release of the evolving H_2 gas. For this case, isopropanol was not a good crystallization solvent for the desired pyrimidine product **3**.[9] Alternatively, when 'wet' MeTHF was used, which was prepared by addition of 4% water to MeTHF, an immediate quench of the excess NaH occurred. Further, the use of MeTHF provided consistent isolation yields and purity verses the addition of isopropanol. As in the deprotonation, the rate of H_2 released during the quench was easily controlled by the rate of addition of the wet MeTHF.[10]

Use of Process Analytical Technology (PAT): Ensuring All NaH Was Quenched. A major concern was ensuring that all of the excess NaH was quenched prior to the addition of copious amounts of water in the extraction stage. An online mass spectrometer was placed in the vent of the reactor to monitor the headspace contents. With a set positive flow of N_2 through the reactor and reactor vent, the mass spectrometer was tuned to measure the ratio of N_2 and H_2 flowing through the vent during the quench. The online mass spectrometer thus indicated the end point of H_2 release. The results from the first batch are depicted in Figure 1. At the start of the addition of the 4% wet MeTHF to the reactor, the mass spectrometer responded with an increase of H_2 detection. The ratio of H_2 to N_2 continued to increase until the rate of addition of the wet MeTHF was slowed. At that point, as expected, a drop in the H_2 off gassing was detected. Continuing the addition of the wet MeTHF at a constant rate, the graph shows a gradual increase and then decrease of the H_2 off-gassing. Since an excess of water *via* wet MeTHF was added with respect to the amount of active NaH remaining in the reactor, the time at which the slope of the plot is at 0 (approximately 2 h) indicated that all the NaH was sufficiently quenched before the addition of wet MeTHF finished after approximately 3 h.

Assuring Purity of Pyrimidine 3: Analytical Analysis. Lastly, we needed to make sure we efficiently and effectively removed the SecuBags polymer from the isolated product. The conversion of reagents to product proceeded as a slurry-to-slurry reaction. The product was isolated by filtration, while the bag polymer remained in solution. An alternative method to remove the bag material from the reaction mixture would be to bring the product into the aqueous layer and separate the organic layer; however, our product could not be pulled into the aqueous layer. Thus, after quenching with the 4% wet MeTHF, the reaction was concentrated via distillation, diluted with an antisolvent, and acidified with 10% HCl solution (Scheme 2).[11] MTBE was chosen as the antisolvent for pyrimidine **3**, as the SecuBag was completely soluble in MTBE. The reaction mixture was filtered, and pyrimidine **3** was washed with MTBE and water. Finally, the dry cake of pyrimidine **3** was tested for SecuBags content.

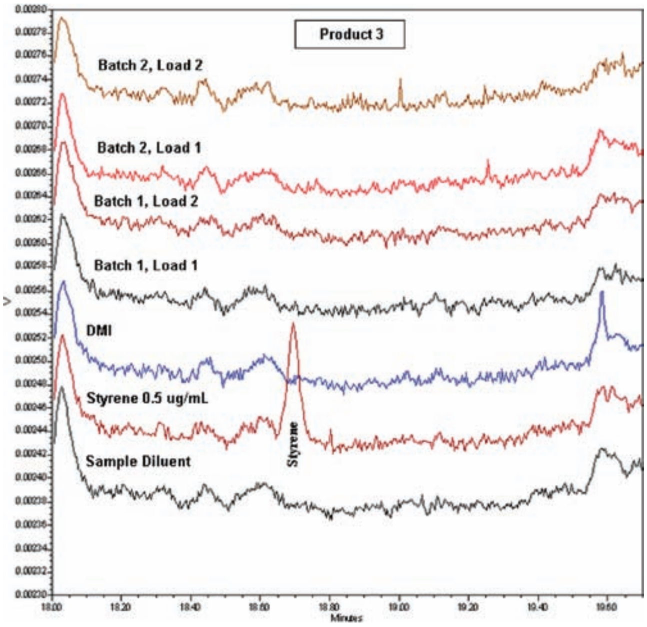


Figure 4. Analysis of batch samples of product **3** using headspace gas chromatography with FID detection to monitor residual styrene.

The SecuBag is made of styrene−butadiene−styrene (SBS) block copolymers. To ensure the SecuBag was sufficiently removed during the filtration, analytical methods were developed to test for residual SecuBag and styrene in the isolated product.

An analytical method that was developed to monitor residual SecuBags polymer used size exclusion chromatography with UV detection at 215 nm. The method resolves SecuBags polymer from the starting materials **1** and **2**, the pyrimidine **3**, Marcol 82,[12] and the diluent (Figure 2). The batch samples were analyzed at a concentration of 0.025 g/mL for pyrimidine **3** with a detection limit of 30 ppm. Analysis of each batch sample of product **3** is depicted in Figure 3. The batch samples contained SecuBags polymer in the range of 120−250 ppm with respect to total weight of sample analyzed, which was well below the ICH recommended level of 1000 ppm.

Residual Styrene in Product. We also evaluated the isolated product **3** for the presence of residual styrene as a result of polymer degradation. Residual styrene would negatively impact the quality of the product, since the ICH allowable level for styrene was 125 ppm based on our projected human dose. Residual styrene was monitored using headspace gas chromatography with FID detection. This method was capable of resolving styrene from ethanol, reaction solvents (MeTHF and MTBE), and the diluent. Analysis at a concentration of 0.1 g/mL for pyrimidine **3** with a detection limit of 5 ppm styrene (0.5 μg/mL) demonstrated that styrene was not detectable in any of the four batches produced by the described process (Figure 4).

CONCLUSION

Sodium hydride was safely utilized on kilogram scale by using a variety of controls: charging the sodium hydride in the dissolvable SecuBags for safe handling, use of online process analytical technology to monitor the hydrogen off-gassing in the process vent during the reaction and workup, and development of analytical methods to monitor residual polymer and potential degradation products from the dissolvable bag in the isolated product. The collaborative effort between process chemistry, pilot-plant operations, early development engineering and process safety, and early development analytical research allowed for a successful scale-up of pyrimidine **3**.

EXPERIMENTAL SECTION

General Procedure. A 60% dispersion in oil of sodium hydride in MeTHF soluble SecuBags (166 mol, 3.2 equiv) was charged to a dry reactor, and MeTHF (70 L) was added. The resulting gray suspension was heated to 75 °C (internal temperature), and a solution of alcohol **2** (52 mol, 1 equiv) in MeTHF (70 L) was slowly added to the reactor followed by the addition of a suspension of chloropyrimidine **1** (52 mol, 1 equiv) in MeTHF (140 L). The batch was held at 75 °C for 15 h and then cooled to 25 °C. A solution of 4% wet MeTHF (42 L) was slowly added to the reactor. After complete addition of the wet MeTHF the batch was concentrated under reduced pressure until 70 L of MeTHF remained in the reactor. Then MTBE (98 L), water (28 L), and 3 M HCl (42 L) were sequentially added to the reactor, and the batch was cooled to 10 °C and agitated for 3 h. The biphasic mixture was filtered, and the filter cake was washed with MTBE (56 L) and then water (56 L). After drying in a vacuum oven at 60 °C for 15 h, pyrimidine **3** was obtained in 75% yield.

ASSOCIATED CONTENT

Ⓢ **Supporting Information.** Comments to a reviewer's question. This material is available free of charge via the Internet at http://pubs.acs.org.

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(2) Urben, P. G. Metal Hydrides. *Bretherick's Handbook of Reactive Chemical Hazards*, 7th ed.; Elsevier: Burlington, MA, 2007; Vol. 2, pp 226−227.

(3) Methanol and acetone are generally used to clean the reactors after a batch run; therefore, trace amounts of each could be present in a clean reactor.

(4) Reaction completion was monitored by sampling through the reactor dip-tube into a small, sealed glass jar. After analysis, the sample was disposed in the lab by quenching with isopropyl alcohol.

(5) Fritz, S.; Feldmann, R. Soluble film for packaging air-sensitive and/or moisture-sensitive hydride reagents. German Patent 196 21 661, Aug. 28, 1997. SecuBags is a registered trademark. At the time of the batch NaH in SecuBags was only available in 1 kg or 5 kg quantities;

however, NaH in SecuBags is currently available in 50 g and 100 g quantities from Aldrich.

(6) The exotherm to which we are referring to is associated with the reaction of solid NaH with moist air or alcohol vapor. Given that the auto-ignition temperature of hydrogen in air is high (585 °C), there is no likelihood of the reaction mass heating to the extent it would ignite the hydrogen, since the solvent heat capacity and heat of vaporization would absorb the energy of either the desired or an undesired reaction prior to reaching this temperature. The risk is that individual particles of solid, finely divided NaH falling through humid air during charging (for example, while being scooped from a drum and dropped into a funnel) can reach a temperature sufficient to ignite either the liberated hydrogen or solvent vapor.

(7) Chemetall Lithium home page: http://www.chemetalllithium.com (accessed on April 19, 2011).

(8) In the event that the project would move forward, we would request from Chemetall Foote smaller quantities of NaH so that there would not be a large excess of NaH left at the end of the reaction. Since this was for a first delivery and it was known that excess NaH did not degrade pyrimidine **3**, we did not request special packaging.

(9) Distillation of the mixed solvent system (isopropanol/MeTHF/water) gave inconsistent isolated yields.

(10) A reviewer asked how we determined what the safe rate of released hydrogen gas was with respect to the batch temperature; our comment can be found in the Supporting Information.

(11) Typically, one would acidify and remove the aqueous layer prior to concentration of the batch; however, in this case pyrimidine **3** was a slurry in MeTHF/water and would not separate from the aqueous layer. Therefore, we could not remove the aqueous layer from the suspended pyrimidine **3**. In an effort to have better control of our solvent ratio for crystallization and having determined via a stress test that our product was stable to the resultant NaOH from the quench, the batch was concentrated prior to the addition of MTBE and aqueous HCl.

(12) Marcol 82 is the mineral oil used to suspend the sodium hydride, and the certificate of analysis states that it meets the EU/USP and FDA purity requirements.Cheplen, M. Chemetall Foote Corp., Kings Mountain, NC, U.S.A. Personal Communication and COA Attachment, 2009.