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Efficient Synthesis of 8-Oxa-3-aza-bicyclo[3.2.1]octane Hydrochloride[†]

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Abstract:

A four-step process to generate 8-oxa-3-aza-bicyclo[3.2.1]octane hydrochloride starting with 5-hydroxymethyl-2-furfuraldehyde is described. Raney nickel-mediated reduction of 5-hydroxymethyl-2-furfuraldehyde afforded 2,5-bis(hydroxymethyl)tetrahydrofuran with a predominantly cis configuration. Conversion of the diol to a ditosylate, followed by cyclization with benzylamine generated the 8-oxa-3-aza-bicyclo[3.2.1]octane core. The title compound was prepared via hydrogenolysis of the *N*-benzyl group with Pearlman's catalyst and isolated as the hydrochloride salt from a mixture of 2-propanol and heptane. The overall yield for the process was 43−64%. An impurity generated during scale up highlighted the need for a strict in-process specification for acetonitrile content prior to performing the final hydrogenolysis. Ethanol conditioning of all processing equipment that had acetonitrile contact prior to the introduction of the substrate stock solution is highly recommended.

Introduction

8-Oxa-3-aza-bicyclo[3.2.1]octane hydrochloride (**1**) was required as a starting material for a program under development at Wyeth. Although commercial sources of this compound were available, the lead time proposed by external vendors was not acceptable to Wyeth's productivity model, details of which have been published recently.[1] To meet the expedited pre-IND timeline, the compound was made in house. This communication describes the route chosen for scale up in order to meet our delivery commitment.

Results and Discussion

The process developed to prepare **1** is shown in Scheme 1 and was based heavily on the work of Wiggins and Cope.[2,3] These early reports on hydrogenation of 5-hydroxymethyl-2-furfural (**2**) to produce 2,5-bis(hydroxymethyl)tetrahydrofuran (**3**) used Raney nickel in diethyl ether at 130−160 °C and 1100−2000 psig hydrogen. Although the reported yield was excellent, (90%) the conditions were not acceptable for scale up in our facility.

Reduction conditions were screened using a parallel, multireactor synthesizer using 10 mL cells with a fill volume of 1.75 mL operating at 600 rpm.[4] The screening focused on conditions that could be used in our facility so all reactions were examined at 60 psig hydrogen and ambient temperature. Multiple types of palladium on carbon and Raney nickel were examined as catalysts in an array of solvents. A summary of the screening is presented in Table 1.

In-process analysis using GC/MS identified an intermediate in the reduction sequence having an exact mass of 130, assigned as the half-reduced furan **7** (Scheme 2), and also revealed that product **3** was formed as a mixture of two isomers.[5] NMR of isolated **3** indicted that the major isomer was consistent with a meso structure, in line with the expected cis product (**cis-3** in Scheme 2). Evaluating the results of our screening, palladium on carbon catalysts were not effective in completely reducing **2** to **3**. A significant amount of intermediate **7** was formed and extending the reaction time from 3 to 24 h did not improve further conversion to **3**.[6]

Contrasting with the palladium on carbon results, the reaction profile was very clean when Raney nickel (entries 11−14) was used as the catalyst. Best results were seen in MeOH, IPA, or a mixture of EtOAc and MeOH, all of which showed complete conversion to the desired product within 3 h at 60 psig hydrogen and ambient temperature. The use of methanol produced the cleanest *cis*-**3** and was chosen for evaluation at a larger scale.

Initial scale-up runs were performed in a 500 mL Parr shaker type hydrogenator. Scaling the reaction up to 10 g of starting material required that the reaction temperature and hydrogen pressure be increased to 60 °C and 70 psig respectively in order to have complete conversion of **2** to **3**. Using these conditions, the reaction was complete within 16−18 h with a Raney nickel charge of 0.3−0.4 mass equivalents.

As the reaction was scaled up further, a Parr 2 L stirred vessel was used. The reduction of **2** to **3** became more sluggish, a demonstration of the significant impact of mass transfer on the reduction. The reaction required 0.8 mass equivalents of Raney nickel in order to reach completion and a new in-process intermediate having a mass of 128 was identified. The new intermediate was assumed to be furan derivative **6** since it did convert to product **3**. Comparing multiple runs conducted in the stirred 2 L pressure reactor with the same lots of starting material, catalyst, solvent ratio, and catalyst charge resulted in

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(1) O'Brien, M. K.; Kolb, M.; Sutherland, K.; McCoy, K.; Pilcher, A. *Chimia* **2006**, *60*, 518–522.

(2) Cope, A. C.; Baxter, W. N. *J. Am. Chem. Soc.* **1955**, *77*, 393–6.

(3) Haworth, W. N.; Jones, W. G. M.; Wiggins, L. F. *J. Chem. Soc.* **1945**, 1–4.

(4) Screening was performed using an Endeavor Catalyst Screening System from Biotage/Argonaut.

(5) ^{13}C NMR supported the 95/5 ratio of isomers determined by GC. See the Experimental Section for line listings of both the major and minor isomer.

(6) Higher reaction temperatures and additional catalyst charges were not evaluated for the reactions that did not go to completion.

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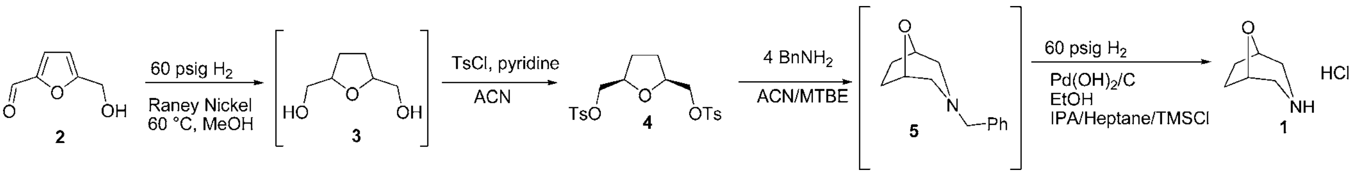
Scheme 1. **Synthesis of 1**



different reaction rates when the agitation speed of the Parr reactor was varied. In fact, at lower agitation (<200 rpm), the reaction did not just slow down but stopped completely.

To gain a more qualitative understanding of the reaction, the hydrogenations were performed in an RC1e equipped with a MP10 glass vessel and a 6-bar rupture disk. Use of this transparent vessel confirmed suspicions that with slow to moderate stirring (<400 rpm), a large portion of the Raney nickel remained on the bottom of the reactor, which led to slow and incomplete conversion of **2** to **3**. At higher agitation (600−700 rpm), the catalyst was lifted off the bottom of the vessel, and complete conversion to **3** was straightforward.[7] When a gas-diffusion stirrer was used (700 rpm), complete conversion required as little as 4 h with 0.8 mass equivalents of Raney nickel.

When the reduction was complete, the catalyst was filtered from the reaction mixture, and the filtrate was concentrated, diluted with acetonitrile, and concentrated again until the methanol to acetonitrile ratio was ≤2:98 (GC area %), and the water content was less than 1% (KF method). Levels of methanol and water above these respective values resulted in incomplete reaction in the next step.

Conversion of diol **3** to ditosylate **4** was performed using slightly modified conditions from those reported by Cope.[2] Our first approach involved addition of solid tosyl chloride to a mixture of **3** in acetonitrile and pyridine. Although complete conversion of **3** to the monotosylate intermediate was achieved, further conversion to **4** was slow. Even after 16 h at ambient temperature, the reaction mixture still contained 20% of the monotosylate intermediate. Increasing the amount of tosyl chloride to 3 equiv and using catalytic dibutyltin oxide accelerated the second step of the process, and complete reaction was observed in less than one hour with 10 equiv of pyridine. The heat output from this reaction was examined in an RC1 and was found to be proportional to the dose of tosyl chloride (Figure 1). The total heat output for the reaction was 152 J/g of reaction mass, corresponding to a ΔT_{ad} of 151 °C. However, in light of the excellent dose-control over the exotherm, the magnitude of the adiabatic temperature rise was not a concern.

Table 1. **Screening Results for Hydrogenation of 2**

trial	catalyst	solvent	SM (%)	intermediate (%)	*trans*-product (%)	*cis*-product (%)
1	5% Pd/C[a]	MeOH	54	14	3	25
2	5% Pd/C[a]	EtOAc	0	50	5	42
3	5% Pd/C[a]	THF	0	44	8	39
4	5% Pd/C[a]	PhMe	29	53	0	12
5	5% Pd/C[b]	MeOH	43	16	5	34
6	5% Pd/C[b]	EtOAc	0	61	5	32
7	5% Pd/C[b]	THF	0	59	0	32
8	5% Pd/C[2]	PhMe	62	38	0	0
9	5% Pd/C[b]	IPA	0	33	10	57
10	10% Pd/C[c]	MeOH	0	33	9	55
11	Raney Ni[d]	MeOH	0	0	5	95
12	Raney Ni[d]	EtOAc[e]	0	0	7	93
13	Raney Ni[d]	THF	61	0	0	39
14	Raney Ni[d]	IPA	0	0	6	94

[a] Water-wet (66 wt % H_2O) catalyst (standard, reduced). [b] Water-wet (51 wt % H_2O) catalyst (eggshell, unreduced). [c] Commercial dry catalyst (uniform, reduced metal). [d] Type 2800, 50 wt % water. [e] Methanol was added to facilitate dissolution of the starting material in EtOAc.

Wyeth's pilot-plant technical group provided feedback that the tin-catalyzed process for the conversion of **3** to **4** had two liabilities: Portionwise addition of solids to a reactor that contained a flammable solvent was not the preferred mode of addition, but more importantly, the use of tin in the reactors of a multipurpose plant would require that specific cleaning and testing procedures be developed to ensure that the processing equipment was free of tin residues at the end of the process.

The reaction conditions were modified such that the acetonitrile stock solution of **3** and 3 equiv of tosyl chloride were combined in a reactor followed by temperature-controlled addition of pyridine to the mixture. Increasing the pyridine charge from 10 to 13 equiv and extending the reaction time to 16 h resulted in complete conversion of **3** to **4**. Quenching the reaction mixture with water resulted in precipitation of the product, which was filtered directly and then rinsed with water and ethanol. Isolation of **4** using these conditions effectively purged the *trans*-ditosylate product that was generated from the *trans*-**3** carried into the tosylation step—there were no impurities detected in the isolated product with a molecular weight of 440.

Evaluation of the modified process in the RC1 provided a heat output of 116 J/g of reaction mass and ΔT_{ad} of 55 °C for the desired reaction (Figure 2). The heat flow profile is the result of multiple exothermic events—presumed activation of the tosyl chloride, the desired reaction, HCl neutralization, and a late exotherm that was observed when stirring was increased to more effectively agitate the thick slurry that had formed. However, the majority of the exotherm occurred early in the pyridine addition profile and was proportional to the dose of pyridine. Having a dose-related exotherm alleviated any concerns regarding control of the exotherm on scale.

As noted above, tosylation of the diol produced a thick slurry in the reactor that prevented quenching the reaction mixture into water. Instead, the reaction had to be quenched by addition of water to the reaction mixture. Evaluation of the quench in the RC1 showed that for the entire water addition, the ΔT_{ad} was 45 °C, and Q_{max} was 90 W. However, as shown in Figure 3, the majority of the heat generated during the quench occurred during the first charge of water. This first charge of water (8 g)

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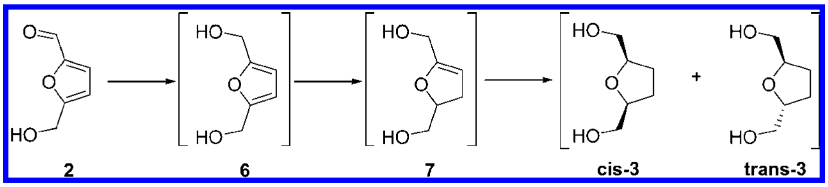
(7) At the suggestion of a reviewer, suspension calculations were performed. The minimum stir speed required in the RC1 to just suspend the Raney nickel (Njs) was calculated to be 1580 rpm. A Dynochem model predicted that the Raney nickel would be fully suspended at stir speeds above 1700 rpm. To have complete reactions in a regime where there was less than optimal power for suspension presumably indicates that kLa was quite high. Dynochem modeling also predicted that at 180 rpm, the Raney nickel would be fully suspended in the pilot-plant vessels. We are grateful to Dr. Albert Schwartz for performing the DynoChem modeling.

Scheme 2. **Proposed Intermediates Detected During Reduction of 2 to 3**



corresponded to 1.8 mol equiv of water, and presumably, the large heat output was due to hydrolysis of the excess tosyl chloride. The second water charge, although 10 times larger in quantity than the first water charge, resulted in a much smaller heat flow. Although some of the heat generated during the addition of water was due to heat of dilution, the magnitude of the heat output, particularly during addition of the first 30 g, is more indicative of a heat of reaction. The heat of dilution appeared to be constant at approximately 20 W, visible during the addition of the last 60 g of water in Figure 3.

The heat-flow data collected during this RC1 experiment alerted us to the potential for a significant temperature rise during the initial part of the quench when the reaction was scaled up to the pilot plant. The operations group was advised to add the initial 10% water charge slowly and gradually increase the addition rate once control of the exotherm was observed. On the pilot-plant scale, the water addition rate gradually increased from 0.2 kg/min to 6 kg/min, once control of the batch temperature was demonstrated.

Scale up of the process to the pilot plant started with 10 kg of **2**. Hydrogen uptake continued for 14.5 h, after which time in-process analysis indicated that there was no starting material or intermediates present in the reaction mixture and the amount of *trans*-**3** formed was 5.4%. The catalyst was removed, and the solvent was exchanged to acetonitrile by concentrating under vacuum (20−30 Torr) with a maximum jacket temperature of 70 °C. Acetonitrile was charged and the vacuum distillation repeated three times (100 kg and 2 × 65 kg charges of acetonitrile). Residual water was 0.7% and 0.2% (in-process target was <0.5%) after the second and third charges, respectively. Residual methanol at the end of the last distillation was 0.01%. The rest of the processing proceeded as expected and generated 28.3 kg of **4** (83% yield). Filtration and drying on a 0.25 m^2 filter/dryer did require extended times—18.5 and 66.5 h, respectively.

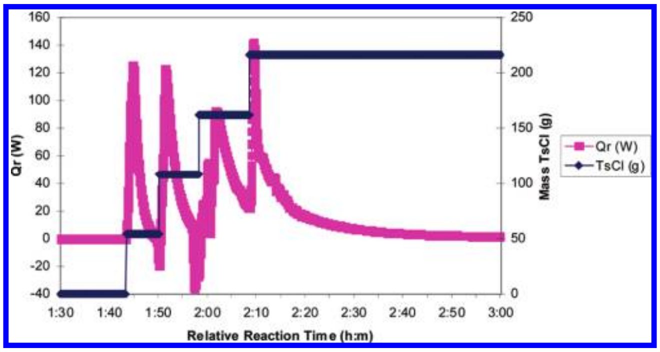


Figure 1. **Heat Flow for 3 to 4: TsCl added to Reaction Mass.**

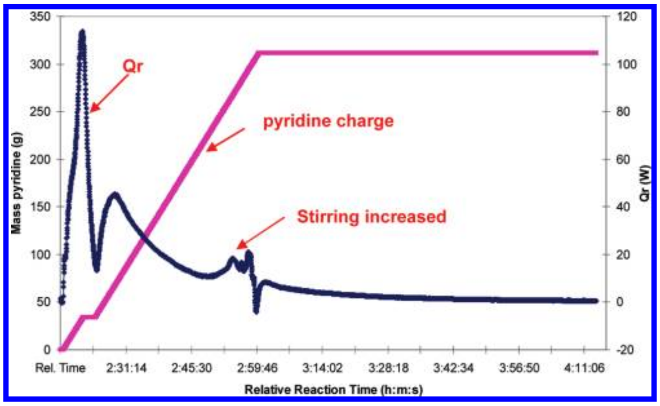


Figure 2. **Heat flow and pyridine dosing profiles for conversion of 3 to 4.**

With a reliable method to generate ditosylate **4** in hand, attention shifted to conversion of **4** to **1**. Although there are reports for the direct conversion of **4** to **1** with ammonia in alcohol (150 °C and 650 psig),[8−10] we were not successful in adapting that chemistry into a process that could be run in our facilities. Instead, a two-step process involving cyclization of the ditosylate with benzylamine followed by hydrogenolysis was developed.[11−13]

Ditosylate **4** was cyclized to **5** in acetonitrile at reflux in the presence of 4 equiv of benzylamine. Attempts to use less than 4 equiv led to incomplete conversion. When the cyclization was complete (<5% ditosylate), 1 equiv of *p*-toluenesulfonic acid was added to scavenge the extra equivalent of benzylamine. The solvent was exchanged to MTBE, the benzylamine/*p*-toluenesulfonic acid salt was removed via filtration, and the solvent was exchanged to ethanol.

The ethanol stream of **5** was combined with Pearlman's catalyst, and debenzylation was performed at 60−65 °C/60−65 psig hydrogen. Some lots of **5** had up to 3% residual benzylamine present, but this did not have a negative impact on the desired reaction as benzylamine was reduced to toluene and ammonia under the reaction conditions. To gain a better understanding of the time required for reaction completion and to evaluate the impact of extended reaction time of product stability, hydrogenolysis of **5** was examined using a MonARC *in situ* FTIR system. The instrument was supplied by Mettler-Toledo and was fitted to the bottom of a standard Parr stirred tank hydrogenator. Starting material **5** had strong IR peaks at 1455, 1166, and 797 cm^{-1}. Hydrogenation led to a decrease in intensity of these peaks with growths at 1402 and 1294 cm^{-1}

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(8) Miller, A. D. U.S. Patent 3,856,783, 1974.
(9) Miller, A. D. U.S. Patent 3,953,596, 1976.
(10) Newth, F. H.; Wiggins, L. F. *J. Chem. Soc.* **1948**, 155–158.
(11) Feurer, A.; Flubacher, D.; Weigand, S.; Stasch, J.-P.; Stahl, E.; Schenke, T.; Alonso-Alija, C.; Wunder, F.; Lang, D.; Dembowsky, K.; Straub, A.; Perzborn, E. WO 03/004503, 2003.
(12) Feurer, A.; Luithle, J.; Wirtz, S.-N.; Konig, G.; Stasch, J.-P.; Wunder, F.; Lang, D.; Stahl, E.; Schenke, T.; Schreiber, R. WO 2004/031186, 2004.
(13) Zask, A.; Kaplan, J. A.; Verheijen, J. C.; Curran, K. J.; Richard, D. J.; Ayral-Kaloustian, S. U.S. 2009/0098086, 2009.

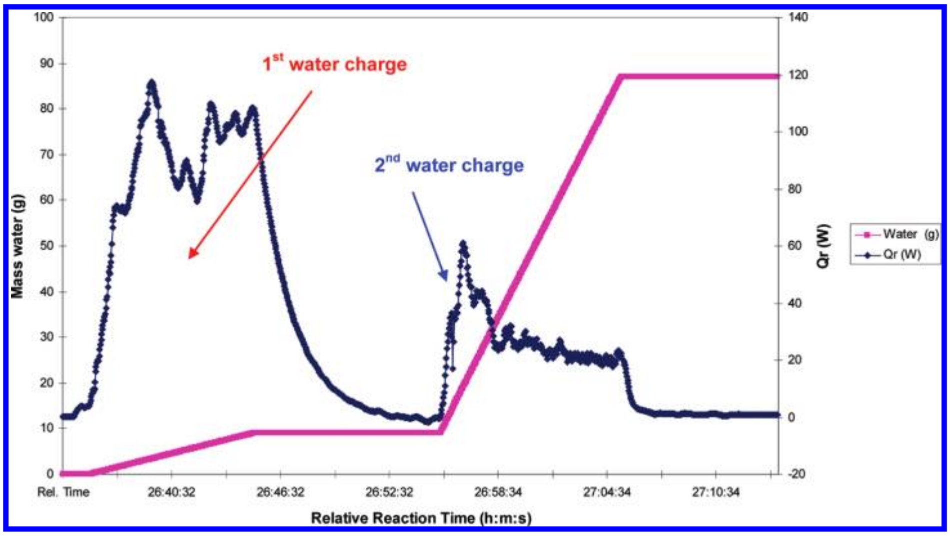

Figure 3. **Heat flow during aqueous quench of 4.**

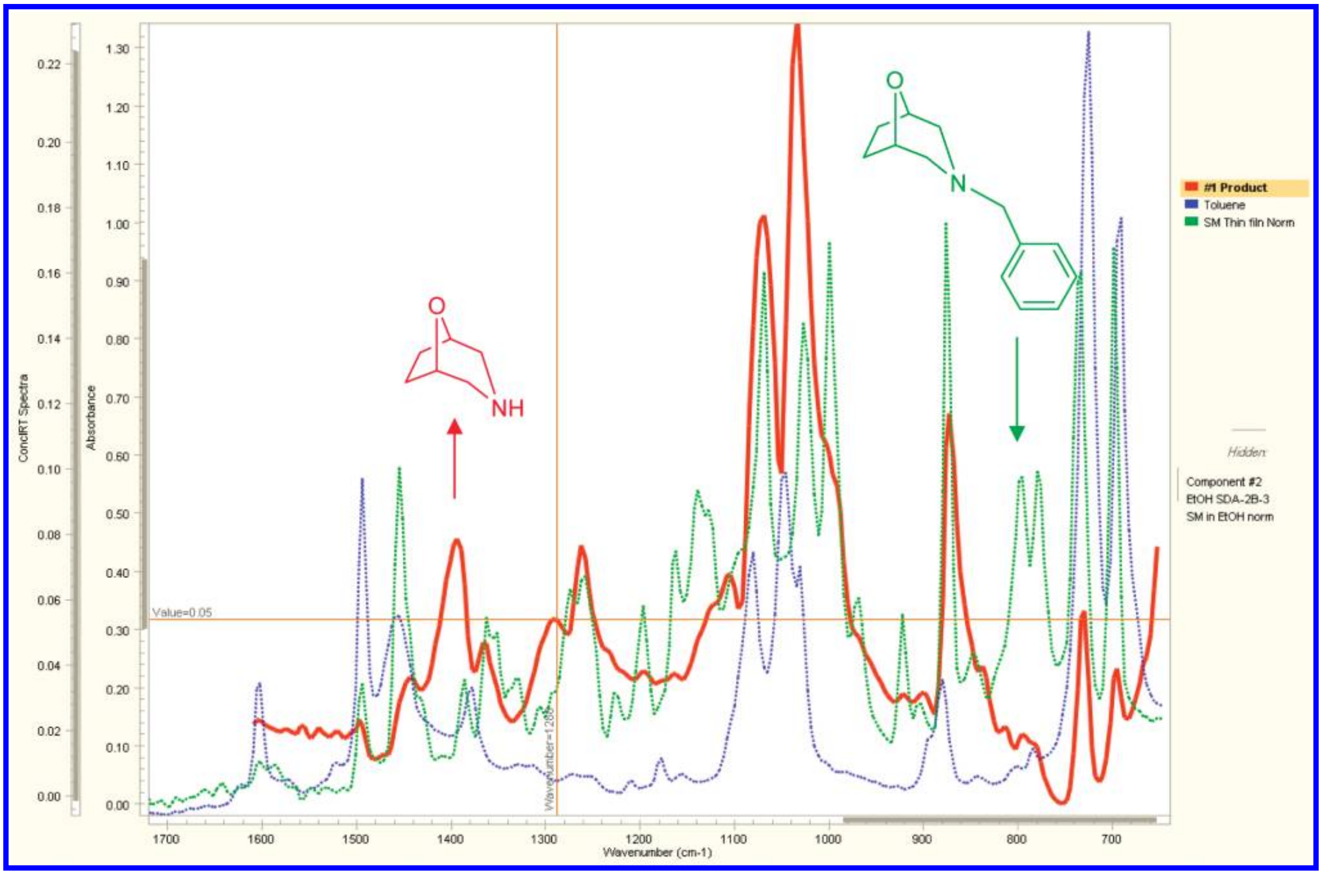

Figure 4. **Chromatograms showing reference spectra of SM and toluene vs the ConcIRT calculated product spectrum.**

(Figure 4). The trend for the hydrogenation followed at 1402 and 797 cm^{-1} is shown in Figure 5. The Sentinal probe, located on the bottom of the tank, was initially blinded by the catalyst. After the vessel was purged of air, the atmosphere was converted to hydrogen and stirring was initiated. An immediate growth for the starting material was detected at 797 cm^{-1} as the catalyst was slowly cleared off the probe. The concentration of starting material at 797 cm^{-1} gradually decreased as the product component grew at the same rate at 1402 cm^{-1} as would be expected for a reaction without an intermediate. Extending the reaction time for hours after the reduction was complete by IR did not result in a significant decrease in the intensity of product at 1402 cm^{-1}, providing evidence that product stability under the reduction conditions was excellent.

Interestingly, toluene was not identified as a separate product of the reaction by the ConcIRT algorithm. However, as shown in Figure 4, the IR spectrum of the product component did show IR bands common to toluene. Since both the product and toluene would appear at the same rate, it is likely that the ConcIRT component spectrum for product is actually a composite spectrum of toluene and the secondary amine product.

Once the hydrogenation was complete, the catalyst was removed and the product was isolated as a hydrochloride salt. HCl was prepared *in situ* by addition of chlorotrimethylsilane

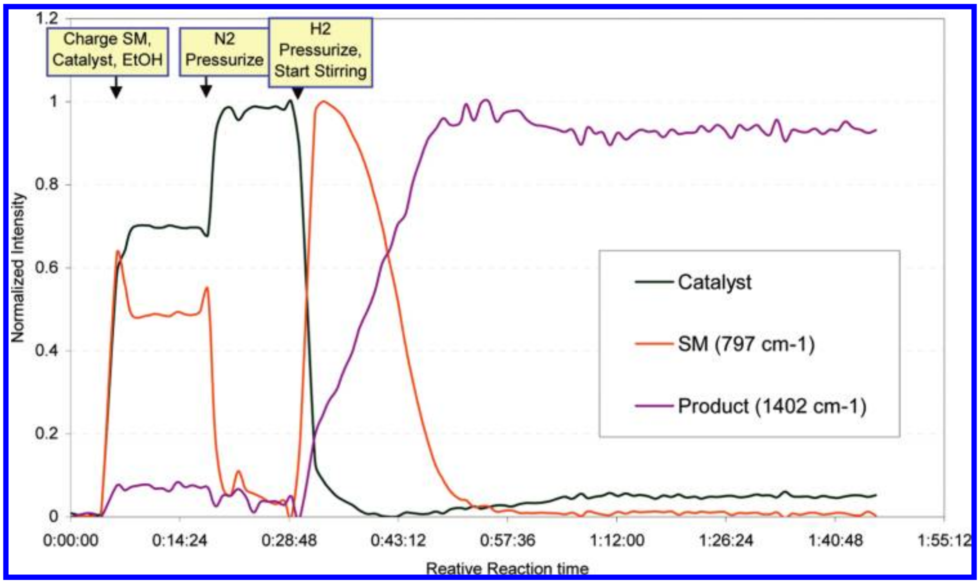

Figure 5. **Relative trends showing normalized IR signals from SM 5 (797 cm^{-1}) and product 1 (1402 cm^{-1}).**

to the solution of **1** that contained some alcohol.[14,15] The solubility of the product hydrochloride salt was quite high in ethanol (23.7 mg/mL) as determined by HPLC using a Charged Aerosol Detector (CAD).[16,17] Losses to the mother liquors would not be acceptable if the product was isolated directly from ethanol. Compound **1** was not soluble in heptane, and addition of IPA up to a 1:1 ratio only increased the solubility to 1.8 mg/mL. On the basis of these data, the solvent was exchanged to heptane after the reduction was complete, and IPA and chlorotrimethylsilane were added to effect precipitation of the product as the HCl salt. Lab yields for the conversion of **4** to **1** were between 60 and 75%.

The process was scaled up to the pilot plant and performed on 27.5 kg of **4**. The cyclization required 48 h on this scale to reach completion compared to 24 h that was observed in the lab. The batch was concentrated at atmospheric pressure, and MTBE was added. At this point in the laboratory, the batch was typically a mobile slurry. In the plant, the slurry was quite thick, and some difficulties were encountered during the transfer—precipitation around the reactor bottom valve complicated the initial transfer of the reactor contents to the filter. However, these problems were resolved, and normal processing resumed. The MTBE solution was then passed through a pad of silica gel, and the solvent was exchanged to ethanol at atmospheric pressure. A sample of the concentrate was assayed and was shown to contain 12.3 kg of **5**, which represented a 97% yield from **4**. The concentrate was diluted with ethanol, combined with Pearlman's catalyst, and reduced at 65−70 °C and 70 psig hydrogen. In-process analysis (GC) after 8 h showed that starting material was not present. However, in addition to the expected product, a new peak was observed that accounted for 17 area %. Data generated using GC/MS and NMR supported that the impurity was the *N*-ethyl derivative of **1**. Precipitation of **1** as the HCl salt did not purge any of the *N*-ethyl derivative, and a total of 8 kg of material was isolated. Fortunately, **1** was an early intermediate en route to the API, and the presence of the impurity did not interfere with the downstream chemistry. The only adjustment was to ensure that the charge of **1** in the next step was corrected for the wt % purity of **1**.

The presence of the impurity, especially at such a high level, was surprising and an investigation into the root cause followed. The sample of the concentrate from the batch that had been tested for in-process assay yield determination had also been examined for residual solvents. GC analysis showed there to be 0.59% and 0.53% acetonitrile and MTBE present respectively—levels that were within the specifications set for the pilot-plant batch based on past laboratory experiments. There was some speculation that the ethylation could have been related to acetaldehyde in the ethanol, either as a contaminate or from oxidation of the solvent.[18] The concentrate from the plant was reduced using the same batch of catalyst and solvent used during the scale-up run. The pilot-plant cycle time, including times for nitrogen purges and hydrogen charges, was mimicked to ensure that prolonged contact of solvent, substrate, and catalysts before the introduction of hydrogen was not the cause of the side reaction. The reductions in the lab were clean—no *N*-ethyl impurity was formed when the same amounts of substrate, solvent, and catalyst were combined and reduced in the laboratory.

The only time we were successful in generating the *N*-ethyl impurity was when acetonitrile was added to the reaction mixture prior to performing the hydrogenation. In fact, ethylation of **1** was quite efficient as the relationship between the level of *N*-ethyl impurity and the molar equivalents of acetonitrile present was found to be linear (Figure 6).[19] In light of our inability to repeat the side reaction when pilot-plant materials

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(14) Connolly, T. J.; Constantinescu, A.; Lane, T. S.; Matchett, M.; McGarry, P.; Paperna, M. *Org. Process Res. Dev.* **2005**, *9*, 837–842.

(15) Luo, F.-T.; Jeevanandam, A. *Tetrahedron Lett.* **1998**, *39*, 9455–9456.

(16) Dixon, R.; Peterson, D. *Anal. Chem.* **2002**, *74*, 2930–2937.

(17) Medved, A.; Dormon, F.; Kaufman, S.; Pocher, A. *J. Aerosol Sci.* **2000**, *31*, S616–S617.

(18) Andersen, D.; Storz, T.; Liu, P.; Wang, X.; Li, L.; Fan, P.; Chen, X.; Allgeier, A.; Burgos, A.; Tedrow, J.; Baum, J.; Chen, Y.; Crockett, R.; Haung, L.; Syed, R.; Larsen, R. D.; Martinelli, M. *J. Org. Chem.* **2007**, *72*, 9648–9655.

(19) Reports to generate oxazolidines from ephedrine and nitriles under comparable reductive conditions are known. See: Henin, F.; Letinois, S.; Muzart, J. *Tetrahedron Lett.* **1997**, *38*, 7187–7190.

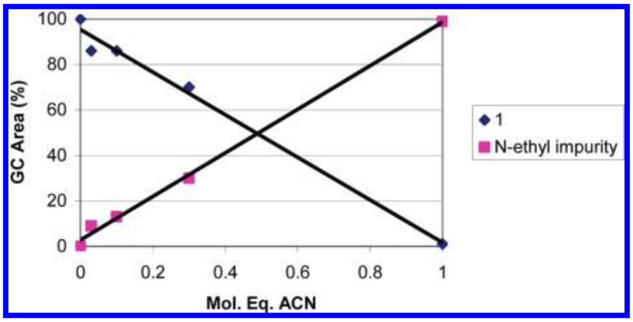

Figure 6. **Relationship between *N*-ethyl impurity level and acetonitrile content.**

and processing times were used, we concluded that the impurity was formed through the inadvertent introduction of deleterious acetonitrile. A review of the batch record from the pilot plant revealed that several pieces of equipment that had acetonitrile contact (pumps, hoses, holding pots, etc.) were used repeatedly during the processing. However, not one piece stood out as the potential source of the acetonitrile contamination. The most obvious point where this could have occurred was during the transfer from the concentrator to the hydrogenation vessel; however, that remains speculation on our part.

Although discovered after the fact, the performance in the pilot plant highlighted the need to have strict in-process controls for the acetonitrile content. It is now recommended to condition all equipment that had acetonitrile contact with ethanol prior to introducing the hydrogenolysis feed-stock solution of **5**. We also recommend that the solvent exchange from acetonitrile to ethanol be continued until the acetonitrile content in the ethanol stock solution is reduced to below the limit of detection using conventional GC-FID.

Conclusion

An efficient synthesis of 8-oxa-3-aza-bicyclo[3.2.1]octane hydrochloride has been developed and demonstrated in the lab. Minor modifications to literature conditions resulted in a process that was easily scaled up. The process described was scaled up to a pilot plant and was executed on a 10 kg scale. The overall strength-corrected yield of **1** from 2-hydroxymethylfurfural was 53%. Unfortunately, upon scale up, some *N*-ethylation of the product was observed during the final hydrogenolysis that depressed the overall yield. It is now highly recommended that the acetonitrile content of the hydrogenolysis stock solution be reduced to below the level of detection when performing the solvent exchange, and all equipment that had acetonitrile contact be conditioned with ethanol before allowing contact with the solution of **4**.

Experimental Section

General. HPLC analysis of the intermediates and reaction monitoring was carried out on a Waters Alliance HPLC with PDA (monitoring at 205 nm) and charged aerosol detectors equipped with a Primesep 200, 4.6 mm × 150 mm, column (5 μm particle size) at 30 °C. Elution was performed with a flow rate of 1.5 mL/min and a gradient method using water/acetonitrile (97:3) w/ 0.025% trifluoroacetic acid (mobile phase A) and acetonitrile (mobile phase B) (initial: 90%A, 2 min, 90%A, 25 min, 10%A). Observed retention times were as follows: TsCl (2.61 min), **1** (5.80 min), benzylamine (7.97 min), toluene (10.87 min), **5** (12.58 min), **4** (16.18 min). Melting points are uncorrected. Commercially available reagents and solvents were used without purification.

(Tetrahydrofuran-2,5-diyl)dimethanol (3). To a 2 L Parr stirred pressure reactor, 5-(hydroxymethyl)furan-2-carbaldehyde (**2**) (50 g, 397 mmol), Raney nickel 2800 (38 g, 1.5 equiv), and methanol (1500 mL, 30 parts v/w)[20] were added. The reactor was flushed with nitrogen three times, then pressurized with hydrogen to 70 psig and adjusted to 60 °C. The reaction mixture was stirred at 600 rpm and 60 °C as the hydrogen pressure was maintained at 70 psig until the conversion to **3** was greater than 95% (AN GC). The reaction solution was cooled to 25 °C and filtered through Celite (50 g, 1 part w/w). The reactor and Celite cake were rinsed forward with acetonitrile (400 mL, 313 g, 8 parts v/w). **Caution! Spent catalyst is pyrophoric! Filtration must be performed under a blanket of nitrogen. Catalyst bed should be rinsed with water and kept water-wet prior to exposure to air and disposal.** The combined filtrate was concentrated to a volume of approximately 200 mL (~4 parts v/w) under vacuum. The concentrate of **3** was methanol/acetonitrile, ratio >2/98. An aliquot of the mixture was concentrated to dryness and provided a clear, slightly yellow liquid: ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.61 (m, 2H), 1.8 (m, 2H), 3.33 (t, J = 8 Hz, 4H), 3.83 (m, 2H), 4.57 (t, J = 8 Hz, 2H) ppm. ^{13}C NMR (400 MHz, d_6-DMSO) (major isomer): δ 27.15, 64.10, 79.69 ppm; (minor isomer) 27.36, 63.64, 79.18 ppm.

***meso*-(Tetrahydrofuran-2,5-diyl)bis(methylene)bis(4-methylbenzenesulfonate) (4).** To the concentrate of **3** in acetonitrile obtained above was added TsCl (227 g, 3 equiv) then pyridine (408 g, 13 equiv). **Caution: Exotherm!** The resulting solution was stirred at 20 °C until the conversion to **4** was greater than 98%. To the reaction mixture was added water (2 kg, 20 parts w/w) **Caution: A significant exotherm is observed during the initial water charge.** The resulting suspension was filtered. The filtered cake was washed with water (2 × 250 g, 2 × 5 parts w/w), then with EtOH (150 g, 3 parts w/w), and dried to afford **4** as a white crystalline solid with 97.2% purity (AN HPLC) in 71% yield from **2**. ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.50 (m, 2H), 1.84 (m, 2H), 2.42 (s, 6H), 3.84 (m, 2H), 3.96 (m, 4H), 7.47 (d, J = 8.0 Hz, 4H), 7.77 (d, J = 8.0 Hz, 4H) ppm. mp 127.0−128.0 °C (lit.[10] 127.5−128.0).

Pilot-Plant Performance. The transformation of **2** to **4** was performed in a 300 gallon vessel set and used the following charges: 5-(hydroxymethyl)furan-2-carbaldehyde (**2**) (9.8 kg), Raney nickel 2800 (7.5 kg), and methanol (158 kg). Following complete reduction, the catalyst was removed and the batch concentrated as the solvent was exchanged to acetonitrile through multiple acetonitrile charges and chases (all unde vacuum). The solution of **3** in acetonitrile was charged to a 300 gallon vessel that contained *p*-toluenesulfonyl chloride (44.5 kg), and pyridine (80 kg) was added. Water was added to

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(20) This reaction can be performed successfully with 8 volumes of methanol to improve throughput. The reaction was demonstrated at this scale to support dilution of the process to the point that both impellers of the dual-flight agitator on the pilot-plant vessel would be submerged when the process was run on a 10 kg scale.

quench the reaction and precipitate the product. Product **4** (28.3 kg, 83% yield) was filtered and dried on a 0.25 m^2 Rosenmund filter/dryer. Filtration and drying of **4** required 18.5 and 66.5 h, respectively.

3-Benzyl-8-oxa-3-azabicyclo[3.2.1]octane (5). To a 5 L reactor was charged **4** (285 g, 0.6469 mol) and acetonitrile (2.28 L). To the resulting slurry was charged benzylamine (277 g, 2.59 mol, 4 equiv) at room temperature. The slurry was heated to reflux (80−85 °C) until the reaction was deemed complete (<2% **4** by HPLC), typically 20−24 h. The reaction mixture was cooled to 40−45 °C, and *p*-toluenesulfonic acid (123 g, 0.4494 mol, 1 equiv) was added. The mixture was heated to reflux, and approximately half of the acetonitrile was distilled out of the mixture. Toluene (700 mL) was charged, and the mixture was cooled to ambient temperature. The solids that were present were removed via filtration, and the collected solids were washed with toluene (2 × 200 mL). The batch was concentrated to approximately one-quarter of its original volume (~400 mL). The mixture was filtered through a plug of silica gel (290 g) and washed with 2 × 250 mL of toluene. The filtrate was concentrated to ~400 mL of residual volume, and MTBE (400 mL) was added. The mixture was allowed to stir at ambient temperature for 15−20 min and was clarified and concentrated to afford **5** as a thick oil, 122 g, 93.5% yield.[21] ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.85 (m, 2H), 1.97 (m, 2H), 2.33 (dd, $J = 11$ Hz, $J = 2$ Hz, 2H), 2.53 (ddd, $J = 11$ Hz, $J = 1$ Hz, $J = 1$ Hz, 2H), 3.45 (s, 2H), 4.27 (m, 2H), 7.29 (m, 2H). A sample of the product was isolated as the hydrochloride salt and used as a reference standard: Purity 99.8% (AN LC), wt % HCl 14.6% (IC, theoretical 15.2%); ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.85 (m, 2H), 2.28 (dd, $J = 8.0$ Hz, 2H), 3.15 (m, 4H), 4.25 (d, $J = 6.0$ Hz, 2H), 4.42 (d, $J = 1.0$ Hz, 2H), 7.40 (m, 3H), 7.75 (m, 2H) ppm, mp 187.1−191.2 °C (lit.[9] 185−185.5 °C).

8-Oxa-3-azabicyclo[3.2.1]octane hydrochloride (1). Compound **5** (50 g) and ethanol (0.225 kg) were combined with Pearlman's catalyst (6.3 g, palladium hydroxide, 50% water-wet) in a 2 L Parr stirred pressure reactor. The system was purged of air with nitrogen three times, and hydrogen was introduced into the system. The hydrogen pressure was adjusted to 60−65 psig, and the reaction mixture was adjusted to 60−65 °C. The reaction mixture was maintained at 60−65 °C/60−65 psig hydrogen until the reaction was complete (<1% **5** AN GC). The pressure vessel contents were cooled to 22 °C, flushed with nitrogen three times and the catalyst was removed via filtration. **Caution: Spent catalyst is pyrophoric! Filtration must be performed under a blanket of nitrogen. Catalyst bed should be rinsed with water prior to exposure to air and disposal.** The filtrate was concentrated by atmospheric pressure distillation. Ethanol was exchanged for heptane until the ethanol level is less than 2% (AN GC). After cooling to ambient temperature, 2-propanol (51 g) was added and the batch adjusted to 5−10 °C. Chlorotrimethylsilane (40 g) was added as the temperature was maintained below 10 °C. Product **1** precipitated, and the slurry was stirred at 5−10 °C for 1−2 h and was collected via filtration. The flask and filter cake were rinsed forward with heptane (100 mL) and the product pulled dry under nitrogen. The product was transferred to a vacuum oven and dried at <50 °C until loss on drying was <2%. Product **1** was isolated as an off-white solid (25 g, 68% yield). Purity 98.1% (GC-FID), wt % HCl: 23.9% (IC, theory 24.2%) ^{1}H NMR (400 MHz, d_6-DMSO) δ 1.90 ppm (m, 2H), 2.10 (m, 2H), 2.81 (d, $J = 8.0$ Hz, 2H), 3.16 (dd, $J = 8.0$ Hz, $J = 1.0$ Hz, 2H), 4.39 (d, $J = 1.0$ Hz, 2H), 9.50 (br, 2H) ppm; ^{13}C NMR (100 MHz, d_6-DMSO) δ 26.48, 46.69, 71.41 ppm; mp 202.6−204.7 °C (lit.[9] 202−204 °C).

Pilot-Plant Performance. The transformation of **4** to **1** was performed in a 300 gallon vessel set and used the following charges: **4** (27.5 kg), benzylamine (26.7 kg) and acetonitrile (173 kg). The reactor contents were adjusted to 80−90 °C and maintained at that temperature until conversion or **4** to **5** was complete (4% **4** remained after 48 h at ~84 °C). When the reaction was complete, a solution of *p*-toluenesulfonic acid (11.8 kg) in acetonitrile (36 kg) was added to the reaction mixture, and the resulting mixture was concentrated at atmospheric pressure from approximately 340 to 115 L. To the concentrate was added MTBE (81.5 kg), the resulting slurry was filtered, and the reactor and cake were rinsed forward with MTBE (122 kg). The filtrates were concentrated at atmospheric pressure from an original volume of approximately 400 L to a minimum stirrable volume (~ 20 L). The batch was cooled to 20−26 °C, and MTBE (20 kg) was added. The mixture was clarified, and ethanol (65 kg) was added to the filtrate. The solution was concentrated at atmospheric pressure from an initial volume of ~115 L to ~40 L. The reactor contents were adjusted to ambient temperature, and ethanol (20 kg) was added. The mixture was combined with Pearlman's catalyst (1.5 kg, 50% water-wet) in an inerted hydrogenation vessel, adjusted to 65 °C and 60−65 psig hydrogen, and maintained under these conditions until the reaction was complete. The vessel was cooled to ambient temperature, the atmosphere was purged of hydrogen, and the catalyst was removed via filtration. The vessel and filter were rinsed forward with ethanol (12.5 kg). The combined filtrates were transferred to a reactor set up for atmospheric distillation and the reactor contents concentrated from an initial volume of approximately 140 L to approximately 114 L. Heptane (143 kg) was charged, and the concentration was repeated as necessary until GC analysis showed there to be NMT 2.0% ethanol present. The mixture was then adjusted to ambient temperature and 2-propanol (12.5 kg) was added. The mixture was adjusted to 4−10 °C, and chlorotrimethylsilane (9.8 kg) was added. The resulting slurry was held for approximately 30 min, filtered on a 0.25 m^2 Rosenmund filter/dryer, rinsed with heptane (2 × 24 kg), and dried under vacuum at 40−50 °C until in-process LOD was NMT 3%. After 20 h, the LOD was 0.2%, and the filter was discharged to afford **1** (8.0 kg, purity 75% (wt %), 64% yield (corrected for wt % purity of product)).

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[21] As noted in the text, we highly recommend that this solvent exchange to ethanol be continued until acetonitrile can no longer be detected by GC before telescoping the ethanol stream of **5** forward. Additionally, all processing equipment that had acetonitrile contact should be conditioned with ethanol before contact with this ethanol stream of **5**.