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Assessment of a Reductive Amination Route to Methyl(3-nitrobenzyl)amine Hydrochloride

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Abstract:

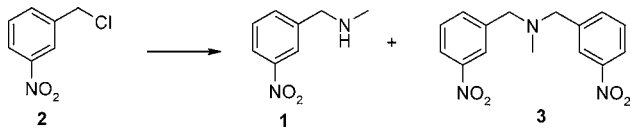
During the development of a sodium borohydride mediated reductive amination of 3-nitrobenzaldehyde with methylamine, studies revealed that partial reduction of the nitro group occurred, and potentially dangerous azo- and azoxy-containing products were generated. Borane-*tert*-butylamine activated with methanesulfonic acid was determined to be a safer reducing agent, and abuse tests on the reduction stage of the process have demonstrated that partial reduction of the nitro group did not occur. Conditions were developed that were suitable for scale-up to a pilot plant.

While supporting the preclinical development of a potential active pharmaceutical ingredient (API), an efficient synthesis of methyl(3-nitrobenzyl)amine (**1**) was required. The routes reported in the literature fall into two categories: alkylation and reductive amination. Both routes were evaluated.

The direct alkylation route (Scheme 1)[1,2] suffered from overalkylation. The ratio of **1** to **3** was 93:7, even when 20 equiv of aqueous methylamine were used. Unfortunately, preparing the hydrochloride salt of **1** did not afford any purification. Based on our need to generate **1** (or the hydrochloride salt) in high purity, the alkylation route was not developed further.

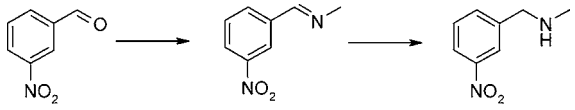
Other preparations of **1** are based on reductive amination of 3-nitrobenzaldehyde (**4**) with methylamine (Scheme 2).[3,4] Meindl reported the successful preparation of several nitro-containing amines, including **1**, via sodium borohydride mediated reduction of the intermediate Schiff base **5**.[3] Billman has also shown that sodium borohydride can be used to reduce nitro-containing imines.[5] We chose to evaluate this route, since sodium borohydride is less expensive than sodium triacetoxyborohydride and sodium cyanoborohydride, two reagents commonly used for reductive aminations of aldehydes and ketones.[6,7]

Scheme 1



2 **1** **3**

Scheme 2



4 **5** **1**

Meindl's reaction conditions (methanol, reflux) were modified slightly, and the reaction was examined in ethanol at ambient temperature. Using these conditions to minimize solvolysis of sodium borohydride generated the desired product in 80% yield with an isolated purity of >99% based on HPLC. The impurities that formed during the reduction did not interfere with isolation of **1** as the hydrochloride salt, and dimer **3** was not formed.

Prior to demonstrating this reaction on any significant scale, parameter-ranging experiments were performed to address the impact of variable reaction temperature, extended reaction time, and reagent stoichiometry. In-process analysis of the reaction mixtures using LC−MS indicated that partial reduction of the nitro group occurred. Compounds detected in variable amounts had molecular masses consistent with structures **6**−**10** (Figure 1).[8] These structures represented molecules with high-energy functional groups, and in our opinion, the formation of even trace amounts of these compounds was a serious concern for scale-up. This observation was surprising, since nitro groups are inert to sodium borohydride unless derivatives of some transition metals (nickel, tin, iron, cobalt, or copper) are present.[9−11] Formation of the impurities could not be eliminated, indicating that the reaction would not be robust or safe to scale up. Extended reaction times, elevated reaction temperatures, and even running the reaction more concentrated caused the impurities to form.

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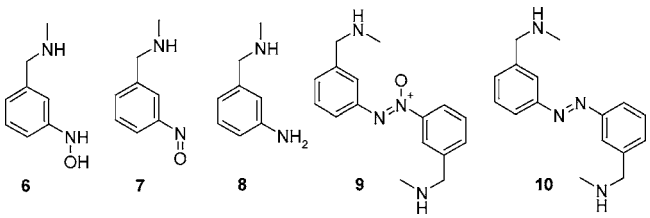

Figure 1. **Proposed compounds detected with LC−MS during $NaBH_4$ reduction of 5.**

Although the direct alkylation route was safer, since reductive conditions were avoided, the projected costs of goods would be high. A large excess of methylamine and another relatively expensive starting material[12] were required, and a significant amount of processing was necessary to provide product of acceptable purity.[13] On the other hand, the potential for reduction of the nitro group with sodium borohydride prohibited scale-up of the reductive amination route. The key to developing a scalable process was in finding a reducing agent capable of selectively reducing the imine functional group in the presence of the aryl nitro group.

Imine **5** could be conveniently formed in yields approaching 90% by adding aqueous methylamine (2.5 equiv) to 3-nitrobenzaldehyde in heptane. The reaction was complete within 30 min, and the product was isolated by filtering the reaction mixture.[14] Alternatively, **5** could be prepared from the aldehyde by generating methylamine in situ from methylamine hydrochloride and sodium hydroxide in a mixture of methylene chloride and water. When the condensation was complete, the organic layer was separated and the solvent was exchanged to hexanes, which caused precipitation of imine **5** in ca. 90% yield.

Diborane and specific borane complexes have displayed selectivity towards the reduction of many functional groups in the presence of a nitro group.[15−17] Of the borane complexes commercially available, borane−amine complexes[18,19] are particularly attractive reagents for large-scale work because many are air-stable solids or liquids.[20−23] The stability of borane−amine adducts, which is a reflection of how tightly the borane is complexed to the amine, does limit their reactivity. Brown has shown that imines can be reduced with various reactive *tert*-butyldialkylamine−borane adducts.[17] Others have shown the same transformation can be accomplished using less reactive complexes such as dimethylamine−borane and pyridine−borane if the reduction is performed in the presence of an acid, which activates the borane−amine complex.[24,25]

For the present reduction, borane−*tert*-butylamine (BTBA) and methanesulfonic acid in methylene chloride were used as the reduction medium. BTBA was selected because the *tert*-butylamine (bp 45 °C) liberated from the reducing agent could be removed during a downstream distillation and would not interfere with the isolation of **1** as the hydrochloride salt. Methanesulfonic acid was used as an activator because it is anhydrous and it formed a soluble complex with imine **5**. The initial reaction conditions involved the addition of 2 equiv of methanesulfonic acid to an equimolar mixture of imine **5** and BTBA in methylene chloride. Acid (2 equiv) was used to protonate both the liberated *tert*-butylamine and the generated amine **3**, thereby preventing the product from complexing with the borane. The reduction was clean and fast when these conditions were used; however there was a significant exotherm, presumably due to multiple simultaneous exothermic reactions, so the order of addition was changed. Addition of methanesulfonic acid (2 equiv) to imine **5** in methylene chloride still caused an appreciable temperature rise, but examination with a reaction calorimeter (RC-1) revealed that the exotherm was immediate and proportional to the dose of methanesulfonic acid. The heat output was significantly attenuated during the addition of the second equivalent of acid (Figure 2) and may be explained by considering that an acid−base reaction has occurred during the addition of the first equivalent of acid only. The heat generated during the addition of the second equivalent of acid is due to dilution of the methanesulfonic acid. For the total addition, the heat output was 77 kJ/mol of **5**, which corresponded to an adiabatic temperature rise (ΔT_{ad}) of 23 °C. Extended addition times were well tolerated, and the combination of **5** and methansulfonic acid was stable in solution for at least 16 h as long as moisture was excluded.

Addition of the mixture of **5** and methanesulfonic acid to a suspension of BTBA in methylene chloride was also significantly exothermic (Figure 3), but once again the exotherm was immediate and directly related to the dose of the imine−acid solution. The profile of the heat output indicated that the reduction was quite fast, since heat evolution ceased when the addition was finished.

When the reduction was complete, the reaction mixture was quenched with dilute aqueous ammonia. Addition of aqueous ammonia to the reaction mixture did not lead to addition control over the heat evolution or off-gas profile (Figure 4). Although the aqueous ammonia was charged over 30 min, the exotherm and off-gassing occurred within the first 5 min. The 400 W exothermic spike was approximately

(12) 3-Nitrobenzyl chloride was only available with a lead time of 12−16 weeks and a cost of ca. $750−$1650/kg.

(13) Mixtures of the hydrochloride salts of **1** and **3** can be separated in a rather labor-intensive procedure that involves dissolving the mixture in water and extracting the dimer hydrochloride salt into methylene chloride. The aqueous solution containing **1** is adjusted to pH 10 and extracted with methylene chloride, and the solvent is exchanged with 2-propanol or ethanol. Dry HCl is added to precipitate the salt, and heptane is added as an antisolvent. Hydrochloride salt of **1** is then filtered and dried.

(14) The condensation is also successful under biphasic conditions using methylamine hydrochloride, sodium hydroxide, and water. A higher charge of water is used in this case to ensure the sodium chloride is extracted into the aqueous layer and does not interfere with the isolation of the imine. These conditions have not been demonstrated on scales larger than 5 g.

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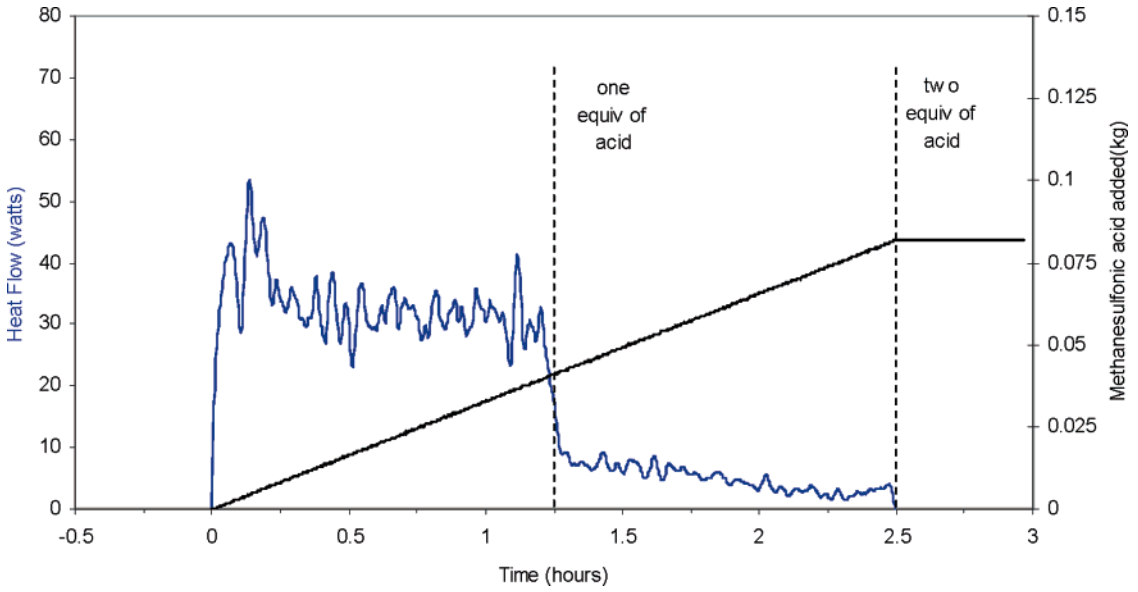

Figure 2. **Heat flow for addition of methanesulfonic acid to imine 5.**

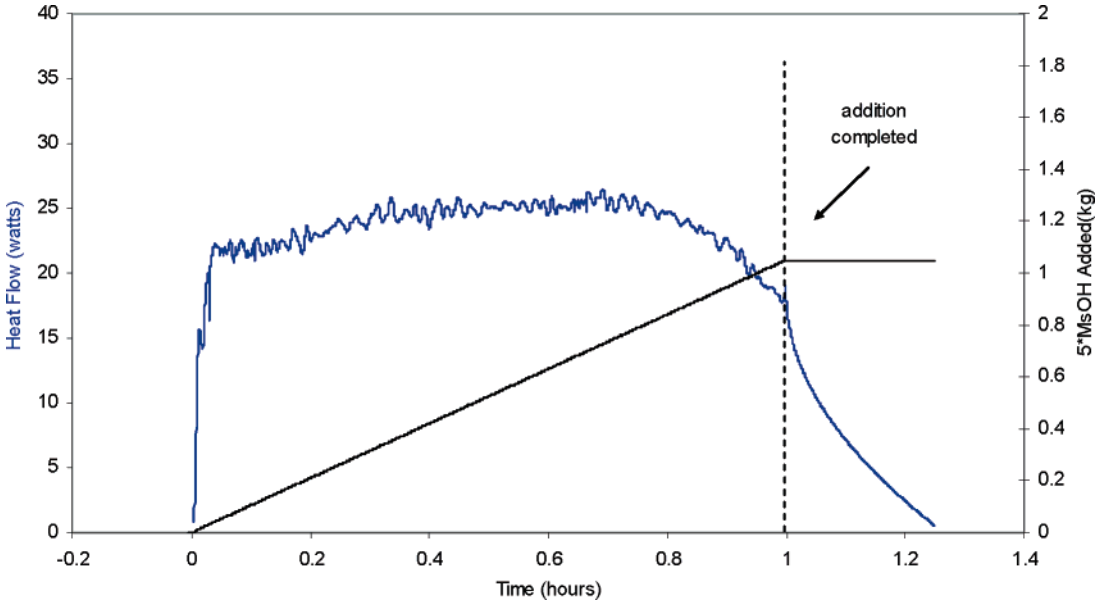

Figure 3. **Heat flow for addition of 5*MsOH to BTBA.**

an order of magnitude larger than the exotherm spikes observed in the other stages of the process. The heat output for the quench was 98 kJ/mol of **5** and corresponded to a ΔT_{ad} of 15 °C. However, considering that the majority of the heat was generated *before* a significant portion of the aqueous ammonia solution was added, a more realistic ΔT_{ad} is 45 °C. This was calculated by estimating the reaction mass when the exothermic event was complete and assuming that the heat capacity of the mixture was similar to the heat capacity of the starting organic solution.

Quenching the reaction mixture into aqueous ammonia resulted in addition control over both the heat generated and the off-gas profile. In this case the heat evolution did occur over the entire quench period (Figure 5) and the calculated ΔT_{ad} of 15 °C is accurate. An induction period was not observed, and the heat output was immediate and constant throughout the course of the quench. The headspace of the reactor was swept with nitrogen and passed through a solution of methanol. Examination of the methanol solution using gas chromatography showed traces of trimethylborate, indicating that borane or diborane was formed in the reactor headspace but not at a level expected to cause any problems on scale.

When the quench was complete, the organic layer was separated and the solvent was exchanged with 2-propanol (IPA). Addition of trimethylsilyl chloride to the mixture of **1** in IPA led to in situ generation of HCl and formation of the hydrochloride salt.[26] Heptane was added to the mixture as an antisolvent, and the hydrochloride salt of **1** was collected by filtration in yields of 90% (from the imine) having a purity of 99% (A% HPLC).

The reduction stage was studied in some detail in advance of scale-up. Addition of imine **5** (1 equiv) and methansulfonic

(26) The use of gaseous hydrogen chloride in the Palo Alto Pilot Plant facility is complicated by the Santa Clara Toxic Gas Ordinance (Ordinance No. NS-517.44, Code of Santa Clara, Division B11, Chapter X).

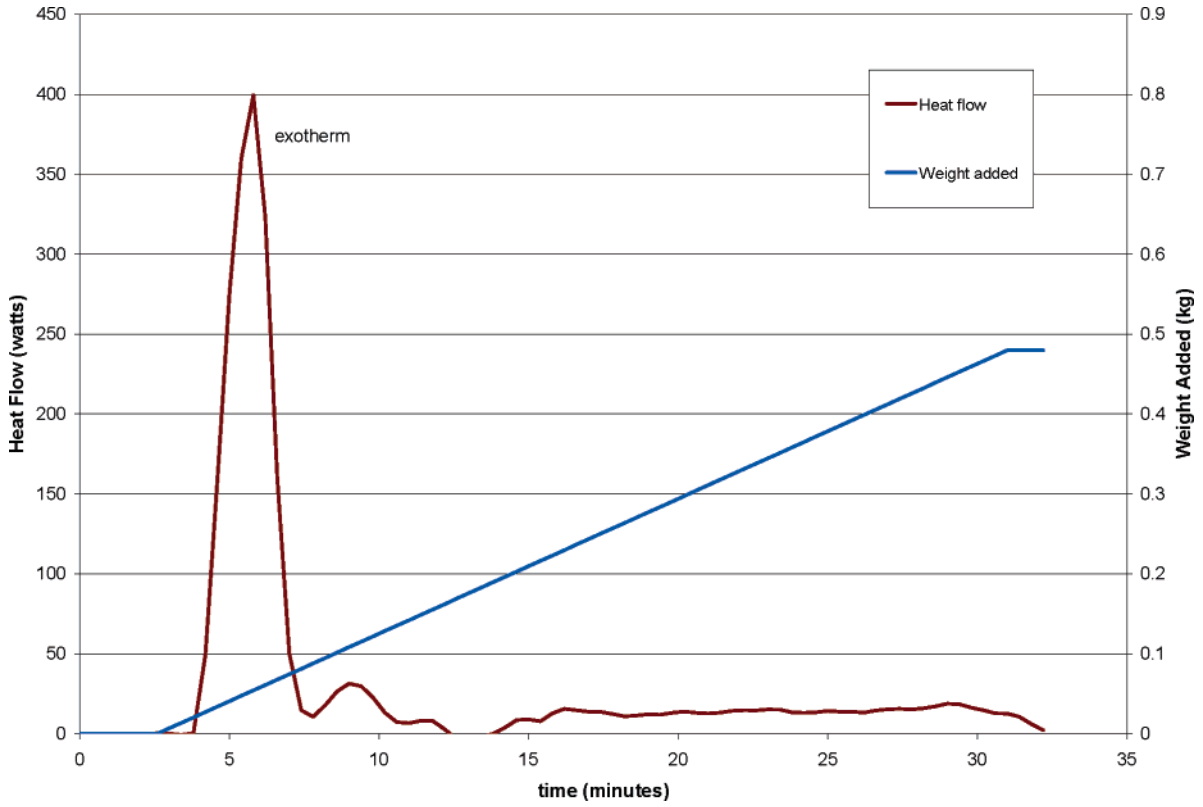

Figure 4. **Quench of reduction: addition of aqueous ammonia.**

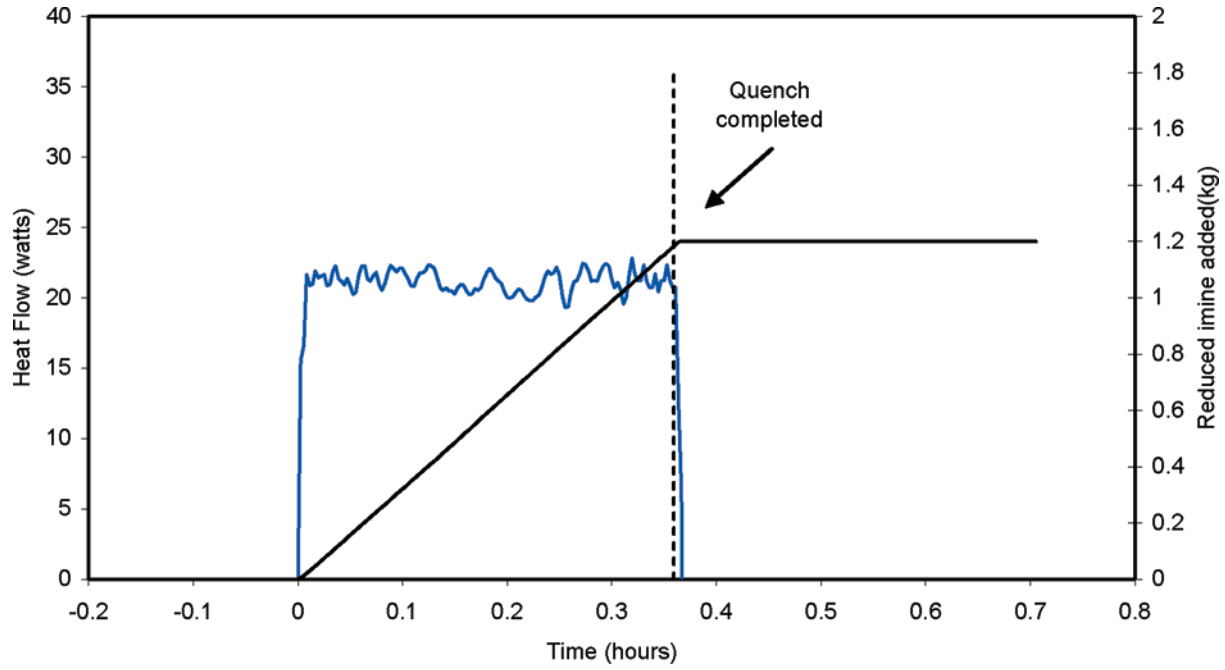

Figure 5. **Quench of reduction: addition to aqueous ammonia.**

acid (2 equiv) to variable amounts of BTBA demonstrated that the reduction was complete when 0.6 equiv of BTBA was used, indicating that roughly half of the hydrides present were available for the reduction. Reducing the amount of acid below 2 equiv caused dimer **3** to form, whereas increasing the amount of acid consumed some of the hydrides, as indicated by incomplete reduction.

The order in which the reagents were added to one another was an important process parameter. When the imine−acid mixture was added to BTBA, the process would tolerate long addition times and complete conversion to **1** was observed when the addition occurred over 18 h. However, when BTBA (0.6 equiv) was added to the mixture of imine and methanesulfonic acid, the reduction stopped at ca. 80% conversion, regardless of whether the addition occurred quickly or slowly. In those cases, an additional charge of BTBA (0.4 equiv) was necessary to force complete reduction. Presumably, addition of the reducing agent to the acidic mixture

led to a competition between reduction of the imine and decomposition of the reducing agent. This mode of addition resulted in reaction conditions with an excess of acid relative to the reducing agent present during the early stages of the addition.

The earlier observation of sodium borohydride causing partial reduction of the nitro group prompted us to examine the BTBA reduction at an elevated reaction temperature (reflux), under an extended reaction time, and in the presence of stainless steel.[27] Under these conditions, reduction of the nitro group was never observed.

Evaluation of a Telescoped Process

A telescoped process was also developed which avoided isolation of the intermediate imine but had another liability. In the telescoped process, imine **5** was formed by adding *N*,*N*-diisopropylethylamine (1.3 equiv) to a mixture of 3-nitrobenzaldehyde and methylamine hydrochloride (1.3 equiv) in methylene chloride. Imine formation was complete within a few hours, after which time water was added to dissolve the generated salts and the organic layer was separated.

It was important to ensure that residual diisopropylethylamine was not carried forward with the organic layer into the reduction stage of the process. Diisopropylethylamine neutralized the methanesulfonic acid that was charged to the solution of imine and led to the formation of dimer **3**. An in-process check (NMR or GC) was inserted at this point to determine the level of diisopropylethylamine present in the organic layer. If diisopropylethylamine was present, then the reactor contents were concentrated, diluted with a high-boiling solvent such as xylene, concentrated under vacuum, and then rediluted with methylene chloride. If the in-process check showed that diisopropylethylamine was not present, then the reactor contents were concentrated and rediluted with methylene chloride.[28] From this point on, the telescoped process and the process described earlier were identical.

Although the telescoped process did eliminate one isolation, the need for tight in-process control with respect to the level of diisopropylethylamine carry-over and the requirement of a high-temperature distillation to remove the diisopropylethylamine were viewed as variable parameters that would complicate scale-up of the telescoped process.[29] The final analysis of the process led to the decision to isolate the intermediate imine and perform the reduction as a separate stage.

(27) Although glass lined reactors would be used during the scale-up of this chemistry, contact with stainless steel could occur, particularly during transfers between reactors where stainless steel fittings are commonly used. We have not explored the impact of vessel contamination with metal catalysts such as Ni and Pd, but based on the work by Couturier, this situation should be avoided, since arylnitro reduction is quite facile and exothermic in protic solvents. See refs 20−22.

(28) It is important to minimize the amount of water carried forward. The methylene chloride solution of imine **5** had 0.02% water (KF method) prior to adding methanesulfonic acid. See ref 29.

(29) Other bases were explored as acid scavengers in the imine forming stage. Triethylamine partitioned in the organic layer and consistently led to dimer formation during the reduction. Incomplete imine formation was observed when *N*-methylmorpholine was used as the base.

Conclusion

Evaluation of an established reductive amination procedure on 3-nitrobenzaldehyde using sodium borohydride revealed the potential for reduction of the nitro group to generate dangerous azo- and azoxy-containing impurities. Borane−*tert*-butylamine activated with methanesulfonic acid was shown to be a safe, reliable alternative for the chemoselective reduction of the nitro-containing imine. Isolation of the imine and a separate reduction stage consistently afforded **1** with high yield and purity. Although a telescoped process was possible, strict in-process controls were necessary to ensure that the isolated product did not contain dimer **3**.

Lab-scale experiments have shown that it is possible to perform the reduction with as little as 0.6 equiv of BTBA and 2 equiv of MsOH. However, the reduction was more robust when 1 equiv of BTBA and 2 equiv of MsOH were used. The reduction has been demonstrated on scales up to 5 kg in the Roche Palo Alto pilot plant.

Experimental Section

General: All reactions were conducted under a nitrogen environment. Borane−*tert*-butylamine was purchased from Callery Chemicals (now BASF). Nitro-containing compounds have the potential to decompose exothermically, with the release of gas. The starting material, intermediate, and final product discussed in this paper were examined using DSC and did not decompose at temperatures below 190 °C. Significant literature exists that highlight the thermal hazards of related compounds.[30] LC−MS was performed on an Agilent 1100 Series liquid chromatograph-mass spectrometer fitted with an atmospheric pressure electrospray ionization interface. The LC method utilized gradient elution on a Zorbax SB-C8 column. The mobile phase was delivered at 1.0 mL/min and consisted of acetonitrile/water acidified with trifluoroacetic acid.

Methyl(3-nitrobenzylidene)amine (5). Method A using aqueous methylamine: Methylamine (80 mL, 40 wt. % in water, 0.92 mol, 2.8 equiv) was added to a mixture of 3-nitrobenzaldehyde (50 g, 0.33 mol) and heptane (500 mL). The biphasic mixture was stirred at ambient temperature for 2 h and then cooled to 0−5 °C, filtered, rinsed with cold heptane (50 mL), pulled dry, and then dried under vacuum at 40 °C. Total yield of product was 48 g, 88% yield, purity 99% (AN GC). δ_H (300 MHz, $CDCl_3$): 8.54 (1H, t, $J = 2.0$ Hz), 8.36 (1H, q, $J = 1.6$ Hz), 8.26 (1H, ddd, $J = 8.0$, 1.2, 1.2 Hz), 8.05 (1H, t, $J = 7.8$, 1.4 Hz), 7.59 (1H, t, $J = 7.9$ Hz), 3.58 (3H, d, $J = 1.6$ Hz) ppm. δ_C (75 MHz, $CDCl_3$): 159.8, 148.6, 138.0, 133.3, 129.6, 124.9, 122.7, 48.2 ppm. Anal. Calcd For $C_8H_8N_2O_2$: C, 58.53; H, 4.91; N, 17.06. Found: C, 57.91; H, 4.78; N, 16.83. Mp 55.1−55.8 °C.

Method B: 3-Nitrobenzaldehyde (100 g, 0.66 mol) and methylamine hydrochloride (67 g, 1 mol, 1.5 equiv) were combined in methylene chloride (500 mL) and water (500 mL). Sodium hydroxide (79.4 g, 50% solution, 1 mol, 1.5

(30) See the information provided for nitrobenzaldehydes, nitrobenzyl compounds, and nitro compounds in Bretherick's Handbook of Reactive Chemical Hazards, 5th edition, P. G. Urben (editor) Butterworth-Heinemann, Boston 1995.

equiv) was added to the mixture as the temperature was maintained below 35 °C.[31] The mixture was stirred at ambient temperature for 2 h, and the layers were separated. The organic layer was concentrated at atmospheric pressure as the solvent was switched to hexanes. The mixture was aged at 45−50 °C for 1 h as crystallization occurred. The resulting slurry was cooled to 5 °C, stirred for 1 h, filtered, rinsed with hexanes, and dried under vacuum to afford 95 g of **5** (87% yield), purity 100% (AN GC).

Methyl(3-nitrobenzyl)amine Hydrochloride: Imine **5** (70 g, 0.43 mol) was dissolved in 700 mL of methylene chloride, and the solution was cooled to <10 °C. Methanesulfonic acid (82.0 g, 0.85 mol, 2.0 equiv) was added (Caution: Exotherm) while the temperate of the mixture was kept below 15 °C. The resulting mixture was added (Caution: Exotherm) to a cooled (5−10 °C) mixture of borane−*tert*-butylamine (37.1 g, 0.43 mol, 1.0 equiv) and methylene chloride (350 mL) while maintaining the reaction temperature below 15 °C. After 1 h, the reaction mixture was quenched into a solution of concentrated ammonium hydroxide (150 mL, 2.5 equiv) and water (350 mL) (Caution: Exotherm and off-gas).[32] The mixture was stirred at ambient temperature, and then the organic layer was separated. The aqueous layer was extracted with methylene chloride (250 mL), and the combined organic layers were concentrated at atmospheric pressure. The solvent was exchanged to 2-propanol (250 mL) by continuing the distillation at atmospheric pressure until the pot temperature reached 72 °C. The solution was cooled to ambient temperature, and chlorotrimethylsilane (46.3 g, 0.43 mol, 1 equiv) was added while the pot temperature was kept below 30 °C. After 1 h, heptane (250 mL) was added, the mixture stirred for 1 h and then filtered. The mixture was rinsed with 2-propanol/heptane (1/1 v/v) and dried under vacuum at 50−60 °C. Total yield was 75.2 g (87% yield). Anal. Calcd For $C_8H_{11}N_2O_2Cl$: C, 47.42; H, 5.47; N, 13.82. Found: C, 47.58; H, 5.45; N, 13.81. Mp 185.7−187.4 °C (lit.[1] 182 °C).

(31) On this scale, the addition required 20 min. A cooling bath was not used.

(32) On a large scale, this quench was done in a vessel that was connected to a system that diluted the off-gas with nitrogen.

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