

Use of DOE for Rapid Development of a Red-Al Reduction Process for the Synthesis of 3,4-Isopropylidenedioxypyrrolidine Hydrotosylate

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Abstract:

Statistical design of experiments (DOE) was used to rapidly optimize Red-Al reduction of an imide to produce, after deprotection and salt formation, 3,4-isopropylidenedioxypyrrolidine hydrotosylate (**1**), an intermediate in the synthesis of Inglistatib. A Red-Al reduction process was successfully scaled to produce multikilogram quantities of **1**, thus demonstrating a safer and more economical process. Further development resulted in an optimized procedure, which not only avoided borane reduction but also allowed the three-step procedure to be performed without isolation of the intermediates, solvent exchange, or distillation.

Introduction

Non-insulin-dependent-diabetes mellitus (NIDDM) is a disease which afflicts about 8–10% of the adult U.S. population. Further, the incidence of NIDDM is increasing.¹ NIDDM is a costly disease that requires improved treatments. One novel approach to the treatment of NIDDM is use of a glycogen phosphorylase inhibitor (GPI); this would provide an orthogonal approach that could complement current therapies.² Classical therapy, such as sulfonylureas, acts by stimulating an increase in the production of insulin in the pancreas. Inhibition of the release of glucose into the bloodstream from the glycogen stores in the liver would provide another mechanism to control blood sugar levels.

The structure of Inglistatib (CP-368,296), shown in Scheme 1, has an important structural subunit, a dihydroxypyrrolidine, which has been the focus of considerable investigation.³ The retrosynthetic strategy (Scheme 1) involves the connection of the protected dioxypyrrolidine, followed by removal of the acetonide to produce the drug candidate. The substituted chloroindole portion has been described in the literature,^{2a} as part of the development of the series of indole-2-carboxamide inhibitors which led to the discovery of CP-368,296.^{2c} A DOE approach was utilized

to speed the development of an improved reduction procedure in which Red-Al ((CH₃OCH₂CH₂O)₂AlH₂Na) replaced the more expensive and more difficult to handle BH₃–THF. The Red-Al process was successfully scaled up to multikilogram scale to support the development of Inglistatib, while laboratory work continued on the development of a three-step-in-one process that avoided isolation of the intermediates, solvent exchange, or distillation.

Results and Discussion

The goal of this program was the generation of a scalable, efficient, and economical process for the synthesis of tosylate salt of 3,4-isopropylidenedioxypyrrolidine (**1**). The initial procedure used for pilot-scale production involved BH₃–THF reduction of imide **2**, followed by hydrogenation and tosylate salt formation (Scheme 2).^{3b,c} Although the BH₃–THF reduction gave an acceptable yield (87.6%), this approach suffered from high cost of BH₃–THF, safety issues of working with BH₃–THF,⁴ and formation of 3–5% of isopropyl ether **4** due to competing reduction of the ketal. The amount of the impurity was significantly higher when borane reducing agent was generated *in situ* from NaBH₄–BF₃ to reduce the cost. Therefore, the development of an alternative imide reduction in a short time period was necessary.

Formation of the undesired isopropyl ether **4** is a result of activation of the C–O bond of the ketal by Lewis acid (BH₃ or BF₃), followed by reduction with BH₃ or NaBH₄. Therefore, use of non-Lewis-acidic reducing agents, such as metal hydride ate complexes, is preferred. Aluminates, such

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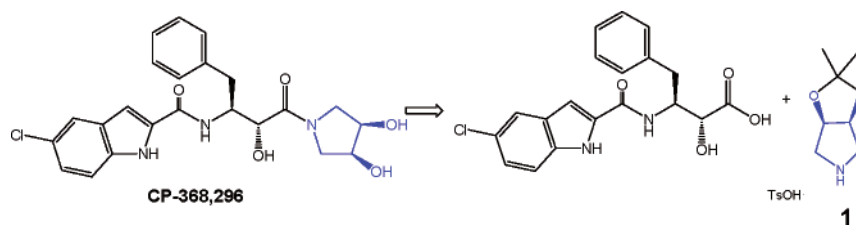
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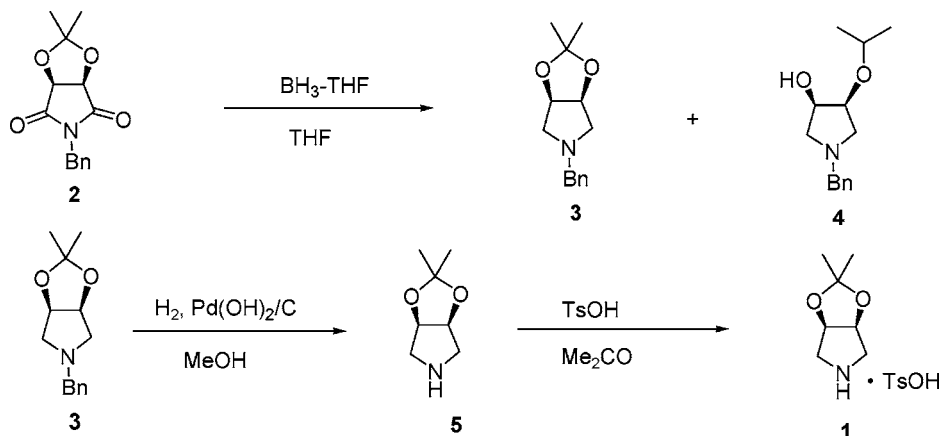
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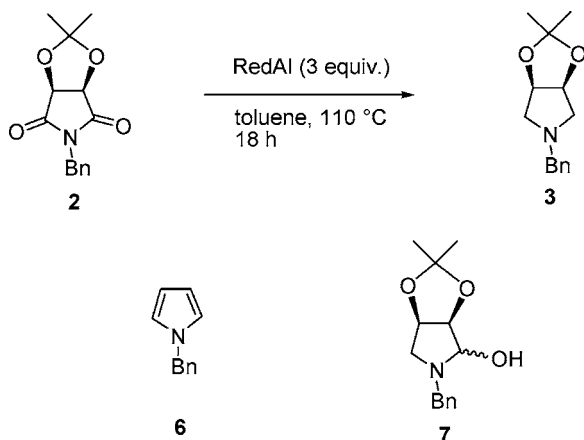
Scheme 1. Partial retrosynthesis of Inglistorib



Scheme 2. Initial synthesis of 1



Scheme 3. Preliminary results of Red-Al reduction



as $(\text{CH}_3\text{OCH}_2\text{CH}_2\text{O})_2\text{AlH}_2\text{Na}$ (Red-Al), are known to be benign to acetals and ketals and at the same time to reduce amides and imides.⁵ Red-Al is also one of the least expensive reducing agents available.

As expected, treatment of imide **2** with Red-Al (3 equiv) in toluene at 110 °C for 18 h afforded *N*-benzylpyrrolidine **3** in 83% yield. Formation of isopropyl ether **4** was not observed.⁶ The product could be easily isolated after basic quench, phase separation, and solvent distillation (Scheme 3).

Although preliminary results looked encouraging, formation of two new impurities in various amounts was observed. Formation of *N*-benzylpyrrole **6** was observed in 4–13% yield, and it was found that higher temperatures and longer reaction time increased the amount of that impurity. The

second impurity, assigned structure **7**, was formed in 6–16% yield.⁷ It appeared that higher temperatures and longer reaction time were needed to convert **7** to the desired pyrrolidine **3**. In fact, **7** was the major compound formed when the Red-Al reduction was performed in THF at 65 °C, and it could be converted to **3** by treatment with excess Red-Al in toluene at 110 °C. It should be noted that the nature of the intermediate **7** was not elucidated until after optimization of the process was completed, due to the demanding project timing.

Interestingly, it was found that formation of *N*-benzylpyrrole **6** could be minimized by changing the addition mode. Addition of a toluene solution of imide **2** to the solution of Red-Al (3 equiv) in toluene at 110 °C over 5–10 min would ensure rapid consumption of the imide and formation of pyrrolidine **3** in 73% purity, without any *N*-benzylpyrrole present. However, formation of 27% of **7** was observed. Since the fine balance between reaction temperature, time, and reagent concentrations needed to be found in a short time frame, statistical design of experiment (DOE) was employed.

Screening Design. A screening design was used to probe the factors of temperature, time, and Red-Al stoichiometry. The outputs for the design were *N*-benzylpyrrolidine **3** purity by LC and GC, area % of *N*-benzylpyrrole, and area % of compound **7** by LC and GC, respectively. A 2^{3-1} fractional factorial experiment with centerpoint replication was performed. It should be noted that the design accounts for only six experiments, therefore allowing evaluation of the “reaction space” in a very short time. It is also noteworthy that if

(5) Seyden-Penne, J. *Reductions by Almino- and Borohydrides in Organic Synthesis*; Wiley: New York, 1997.

(6) Theoretically, 2 equiv of Red-Al is necessary for the reduction. However, excess reagent was necessary to drive the reaction to completion.

(7) Investigation of the structure of the partial reduction product supported the amide or hydroxypyrrolidine; in either case, the excess Red-Al continues the reduction to the desired product.

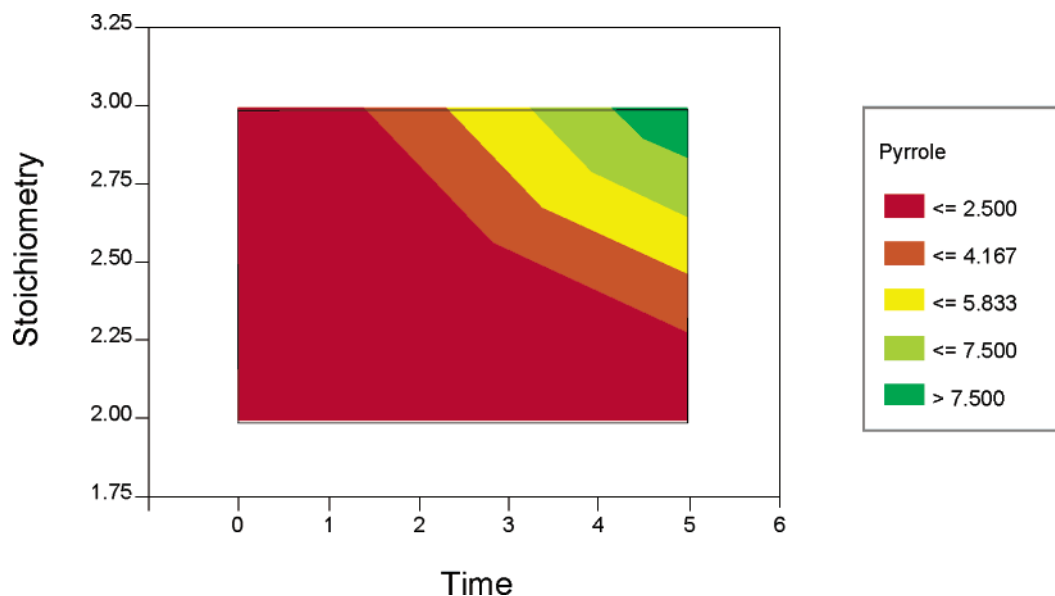
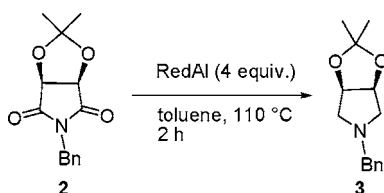


Figure 1. Area % of *N*-benzylpyrrole as a function of time and stoichiometry.

Scheme 4. Optimized conditions for reduction of **2**

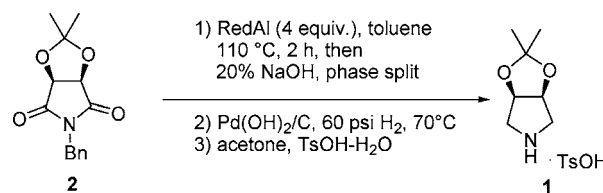


the results of the 2^{3-1} DOE were insufficient, an additional four experiments could be performed to convert to a 2^3 DOE.

The results of the experiments revealed a statistically significant correlation between reaction temperature and *N*-benzylpyrrolidine **3** purity by GC (Prob. $> F = 0.0162$). Additionally, the area % of *N*-benzylpyrrole was dependent upon temperature, time, and Red-Al stoichiometry in a statistically significant way (Prob. $> F = 0.0295$). Figure 1 shows the contour plot for area % of *N*-benzylpyrrole as a function of time and Red-Al stoichiometry.

An optimized procedure for the conversion of **2** to **3** was rationally designed in light of the mathematical modeling of the system. Extrapolation of the functions that describe dependence of the yield of the product and byproducts on the reaction time and Red-Al concentration, allowed us to propose that use of 4 equiv of Red-Al (effectively higher Red-Al concentration) and 2 h reaction time at 110 °C should result in complete consumption of the intermediate hydroxypyrrolidine **7** while still keeping the amount of *N*-benzylpyrrole **6** at a minimum. The large red area, as shown in Figure 1, quickly showed how the level of *N*-benzylpyrrole **6** could be controlled by the stoichiometry and time of reaction. Indeed, the reaction under these conditions provided the desired compound **3** in 93% yield with a purity by GC of 99% (Scheme 4). Pyrrolidine **3** prepared this way could then be deprotected by hydrogenation in MeOH and converted to the tosylate salt **1** by treatment with *p*-TsOH–H₂O in acetone or MIBK. It should be noted that DOE was used in this case merely as a guide (allowing evaluation of the reaction trends) and in combination with additional information to make predictions about optimal conditions. Thus,

Scheme 5. Pseudo-one pot procedure for the synthesis of **1**



DOE worked along with chemical intuition to minimize the levels of impurities and to improve the yield of the Red-Al process.

During the scale-up of the Red-Al procedure developed above, laboratory work continued to provide further process streamlining.

Streamlined Laboratory Procedure: The possibility of using toluene for all three synthetic steps from **2** to **1** was then explored as a means of simplifying the process and reducing the overall cycle time. It was found that hydrogenation of a toluene solution of pyrrolidine **3** after Red-Al reduction, basic workup, and phase separation (under 60 psi H₂ at 70 °C in the presence of Pd(OH)₂/C 10 wt %) afforded the desired deprotected pyrrolidine **5**. The reaction mixture was filtered, diluted with acetone (to ensure solubility of *p*-TsOH–H₂O), and treated with a solution of *p*-TsOH–H₂O in a minimal amount of acetone. Filtration afforded tosylate **1** in 76–78% yield (after three steps based on **2**) with >98% purity as judged by ¹³C NMR and >99% purity of the free-based pyrrolidine by GC (Scheme 5).

Thus, tosylate **1** can be prepared in an efficient way, avoiding lengthy solvent distillations and the use of borane–THF reducing agent; it can then be isolated directly by filtration.

Conclusions

Use of DOE allowed rapid optimization of a procedure for Red-Al reduction of imide **2** to produce *N*-benzyl-3,4-isopropylidenedioxypyrrolidine **3**. The optimized procedure was identified in only six experiments. It is noteworthy that the optimal conditions could be identified without complete

information on the structure of one of the impurities, compound **7**, as it was possible to minimize its formation. As a result, a better, safer,⁴ and cost-effective⁸ procedure was developed to replace a borane reduction with Red-Al. The process was then successfully scaled to produce multi-kilogram quantities of **1** for our program. The process was further streamlined, in the laboratory, to perform the reduction, deprotection, and salt formation to form **1** without any solvent removal, exchange, or isolation of intermediates.

Experimental Section

Pilot-Scale Production of *meso*-*N*-Benzyl-3,4-isopropylidenedioxypyrrolidine (3**).** A total of 44.7 kg (171.1 mol) of **2** and 457 L of toluene were combined in a 500-gallon glass-lined reactor, and the mixture was warmed to between 50 and 60 °C until an almost complete solution had been achieved. The resulting solution was filtered to remove some trace insolubles and then added to a solution of 220.0 kg of Red-Al (65 wt % solution of sodium bis(2-methoxyethoxy)-aluminum hydride in toluene), which was in 112 L of toluene, over 40 min at 20–35 °C stirring in a second 500-gallon glass-lined reactor. The resulting solution was heated to reflux for about 4 h and was then cooled to room temperature. To the reaction solution was slowly added a solution of 268 kg of a 50% aqueous solution of sodium hydroxide in 505 L of water, while carefully maintaining an internal temperature of between 10 and 30 °C. Following addition, the mixture was stirred for about 20 min, and then the layers were allowed to settle. The organic layer was separated and washed twice with 253-L portions of water, and the toluene was removed by atmospheric distillation, displaced with methanol (97 L), and concentrated to a thin oil. The resulting oil was employed directly in the next step.

Pilot-Scale Production of *meso*-3,4-Isopropylidenedioxypyrrolidine Hydrotosylate (1**).** Following three nitrogen purges and testing for residual oxygen, 20% palladium hydroxide on carbon (50% water wet) was charged to a 300-gallon Hastelloy, nitrogen-purged, hydrogenation vessel. Compound **3** [*meso*-*N*-benzyl-3,4-isopropylidenedioxy-2,5-pyrrolidine], obtained above, 79.8 kg (342 mol, yield in step 1 above assumed to be 100% due to product being an oil),⁹ was charged followed by 387 L of methanol. The suspension was hydrogenated at 50 psig for ~7 h at 15–30 °C. The catalyst was then removed by filtration, and the line and filter were rinsed with an additional 78 L of methanol. The methanol was displaced with 554 L of methyl ethyl ketone by distillation at atmospheric pressure, and then the solution was filtered. *p*-Toluenesulfonic acid monohydrate (65.1 kg, 342 mol) was dissolved in 198 L of methyl ethyl ketone and then combined with the reaction mixture to form the salt. The resulting slurry was stirred with cooling, and the

product was collected by filtration, giving 89.7 kg (284 mol, 83.1% yield over two steps). Purity: 96.1% by GC (HP-5 5% phenylmethylsiloxane 30 m × 0.32 mm, flow of 2.2 mL/min with flame ionization detector at 250 °C). ¹H NMR (400 MHz, CDCl₃): 9.46 (1H, br s), 9.26 (1H, br s), 7.72 (2H, d), 7.18 (2H, d), 4.81 (2H, m), 3.62 (2H, d of d), 3.29 (2H, m), 2.36 (3H, s), 1.83 (2H, ex. s), 1.45 (3H, s), 1.27 (3H, s).

Improved Laboratory Procedure

***meso*-*N*-Benzyl-3,4-isopropylidenedioxypyrrolidine (**3**).** Toluene (25 mL) was charged to a 500-mL four-neck round-bottom flask equipped with a temperature controller, a N₂ inlet, a condenser, and a mechanical stirrer. Red-Al (46 mL, 65% solution in toluene, 4 equiv) was placed in the flask. The solution was heated to reflux (110 °C). In a separate vessel, a mixture of **2** (10 g, 1 equiv) and 100 mL of toluene was heated to 50 °C to form a cloudy solution. The solution of imide **2** was added to the refluxing Red-Al solution over a 5-min period using an addition funnel. The reaction mixture was stirred at 110 °C for 1 h 50 min. GC and HPLC analyses indicated complete consumption of starting imide **2** and intermediate **7**, and formation of pyrrolidine **3**. The reaction mixture was cooled to 0 °C and quenched with 20% sodium hydroxide (150 mL), while keeping the temperature below 10 °C. The aqueous layer was separated and extracted with 2 × 50 mL of toluene. The combined organic phase was washed with 3 × 50 mL of water, filtered, and concentrated to afford pyrrolidine **3** (8.26 g, 93% yield; purity: 95 area % by HPLC, 99 area % by GC).

***meso*-3,4-Isopropylidenedioxypyrrolidine Hydrotosylate (**1**).** Imide **2** (10 g) was reduced as described above to afford, after work-up and filtration, a toluene solution of **3** (240 mL overall volume), which was used further without solvent removal. The solution was subjected to hydrogenation in two batches as follows. A 120-mL portion of the toluene solution and the slurry of Pd(OH)₂/C (10 wt %, 0.5 g) in toluene (10 mL) was charged into a hydrogenation apparatus. The system was purged three times with hydrogen (50 psi), pressurized to 60 psi H₂, and stirred at 70 °C for 29 h, after which GC of an aliquot indicated complete consumption of **3** and formation of **5**. The reaction mixture was cooled to room temperature, depressurized and filtered through Celite, and the catalyst was washed with toluene (40 mL). The second portion (120 mL) was hydrogenated in a similar manner (0.5 g Pd(OH)₂/C, 20 h) and filtered through Celite, and the catalyst was washed with acetone (60 mL). The combined solution was diluted with acetone (155 mL). A solution of *p*-TsOH–H₂O (1.1 equiv, 8.01 g) in acetone (18 mL) was added with stirring. The mixture was kept at room temperature for 1 h. The precipitate of **1** was filtered, washed with 50 mL of 60:40 toluene–acetone mixture, and dried in a vacuum to afford 9.37 g of product (78% yield).

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(8) Evaluation of the bulk cost of borane/THF and Red-Al in toluene showed that the cost per hydride equivalent was 4–5 times higher with borane/THF.

(9) Due to the relative size of the reaction vessels, two lots of compound **3** were prepared and combined for use in this procedure.