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Process Development and Scale-up of a Selective α_1-Adrenoceptor Antagonist

Terrence J. Connolly,* Michael Matchett, and Keshab Sarma

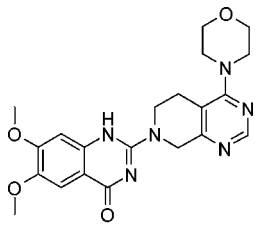
NCD Chemical Services, Chemical Development, Roche Palo Alto LLC, 3431 Hillview Avenue, Palo Alto, California 94304, U.S.A.

Abstract:

A synthetic route to a potent and selective α-1-adrenergic receptor antagonist has been developed and demonstrated in a pilot plant. The route has been used in two pilot plant campaigns and has produced RO3203546 in 2.3 and 12.0 kg batch sizes. The first pilot plant campaign focused primarily on the end-game of the process with particular emphasis on the development of a method to isolate the active pharmaceutical ingredient (API). The second pilot plant campaign allowed front-end process improvements to be demonstrated. The reiterative process improvements resulted in an economical process with improved throughput and product quality when compared to the original discovery synthesis.

Introduction

Benign prostatic hyperplasia (BPH) is the most common cause of voiding dysfunction in men and as such is one of the most frequent causes of lifestyle disruption. Clinical studies have shown α-1-adrenoceptor antagonists to be effective in relieving symptoms associated with BPH.[1] Subtypes of the α-1-adrenergic receptors are known (α_{1A}, α_{1B}, and α_{1D}).[2,3] The α-1 blockers currently being used to treat BPH are nonsubtype selective and have the potential to cause significant cardiovascular side effects such as postural hypotension and dizziness. These side effects can be dose limiting, which may sacrifice efficacy. RO3203546 (**1**) has shown particular promise as an α-1 antagonist that displays selectivity at the α_{1A} and α_{1B} subtypes.[4] Larger quantities of **1** were required to support preclinical studies. The synthetic route developed by discovery chemistry was evaluated by process chemistry and refined into a process that delivered 2.3 and 12.0 kg lots of RO3203546.



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Results and Discussion

Review of Medicinal Chemistry Route. The route used by the medicinal chemistry group to generate RO3203546 is shown in Scheme 1. To generate pyrimidinone **3**, discovery chemists combined **2**,[5] formamidine hydrochloride, and sodium methoxide in methanol and heated the mixture at reflux until the reaction was complete (ca. 16 h). Although the reaction was straightforward, the workup was rather cumbersome and involved isolation of hydrochloride salt **3** in three crops for a combined total yield of 85%.

The second stage involved conversion of **3** to chloropyrimidine **4**. The discovery protocol involved adding **3** in portions to phosphorus oxychloride (8 mL/g of **3**) which contained substoichiometric (0.6 equiv) *N*,*N*-diethylaniline. The reaction mixture was heated at 85−105 °C for 17 h. Excess $POCl_3$ was removed by distillation, and the residue was quenched into water, treated with base, and extracted. Chloropyrimidine **4** was isolated as a concentrate from a mixture of methylene chloride and toluene. The yield for this step, based on the weight of the concentrated residue, was 79%. Crude chloropyrimidine **4** was coupled with morpholine in 2-propanol and afforded product **5** in a yield of 45%. The yield was increased to 70% by chromatography of the concentrated mother liquor.

Discovery chemists removed the benzyl protecting group of **5** with hydrogen under medium pressure (40 psi) in methanol using palladium on carbon as the catalyst. The reaction required up to 6 days to reach completion, after which time the catalyst was removed, the solvent was replaced with water and the free base of **6** was extracted from the neutralized aqueous layer via continuous extraction with methanol and methylene chloride. The organic layer was concentrated to afford **6** in 94% yield as a yellow oil.

Chloroquinazolinone **7** was generated from dichloride **8**[6] via a partial and selective hydrolysis using aqueous sodium hydroxide (13 equiv.) in dioxane (Scheme 2). An insoluble solid formed during the hydrolysis which was removed by an in-line filtration. The pH of the filtrate was adjusted to 5 with acetic acid, and **7**, which precipitated, was isolated in 74% yield.

* Correspondence should be addressed to this author at Roche Palo Alto LLC, Mailstop R4-122, 3431 Hillview Avenue, Palo Alto, CA 94304, U.S.A. E-mail: terrence.connolly@roche.com.

(1) Caine, M.; Raz, S. *Br. J. Urol.* **1976**, *48*, 255−263.
(2) Schwinn, D. A.; Lomasney, J. W.; Lorenz, W.; Szklut, P. J.; Fremeau, R. T.; Taqny-Feng, T. L.; Caron, m. G.; Lefkowitz, R. J.; Cotecchia, S. *J. Biol. Chem.* **1990**, *265*, 8183−8189.
(3) Schwinn, D. A.; Johnston, G. L.; Page, S. O.; Mosley, M. J.; Wilson, K. H.; Worman, N. P.; Cambell, S.; Roock, M. O.; Furness, L. M.; Parry-Smith, D. J.; Peter, B.; Beiley, D. S. *J. Pharmacol. Exp. Ther.* **1995**, *272*, 134−142.
(4) Becker, C. K.; Caroon, J. M.; Melville, C. R.; Padilla, F.; Pfister, J. R.; Zhang, X. WO 02/053558 A1, 2002.
(5) Compound **2** is commercially available in small quantities from Acros and SAF.
(6) Compound **8** is commercially available from Acros, Lancaster, and SAF.

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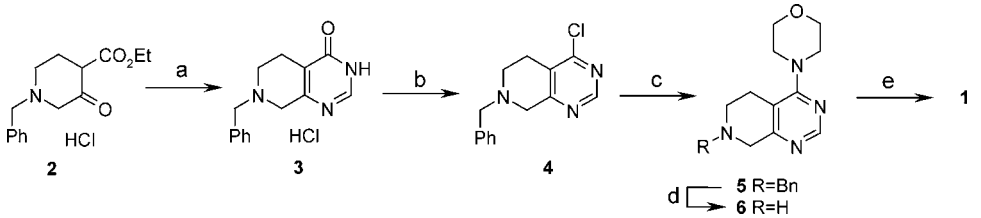
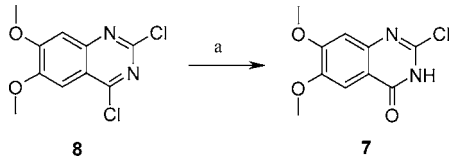
Scheme 1[a]



[a] Reagents: (a)(i) formamide hydrochloride, NaOMe, MeOH; (ii) HCl; (b) $POCl_3$, $PhN(Et)_2$; (c) morpholine, IPA; (d) H_2 (40 psi), Pd/C, MeOH; (e) **7**, $MeOCH_2CH_2OH$.

Scheme 2[a,b,c]



[a] Discovery route: (i) NaOH, 1,4-dioxane, H_2O; (ii) HOAc. [b] Pilot Plant 1: (i) NaOH, THF, H_2O; (ii) HOAc. [c] Pilot Plant 2: (i) KOH, THF, H_2O; (ii) HOAc.

Crude **6** was combined with an equivalent of **7** in methoxyethanol, and the mixture was heated at 95 °C for 48 h. RO3203546 precipitated from the reaction mixture as the hydrochloride salt, but the isolated solid contained an equivalent of methoxyethanol. Attempts to remove the methoxyethanol by washing the solid with hot ethanol reduced but did not eliminate the methoxyethanol and led to the incorporation of ethanol in the solid.

The sequence developed by the discovery chemists was an excellent synthetic route. It provided RO3203546 in a convergent manner, and yields for each step were quite respectable. There was minimal chromatography, and several of the intermediates were solids. However, there were aspects of the synthesis that required attention before this sequence could generate significant quantities of API. The process used toxic solvents (e.g., 1,4-dioxane[7] and 2-methoxyethanol[8]) which are undesirable for large scale work. In several instances, the workups would be rather difficult or inefficient on-scale (e.g., continuous extraction and isolation of multiple crops of product). The long reaction times and high solvent ratios would limit throughput and lead to long cycle times for several stages of the process. Some of the reagents used were either difficult to procure[9] or difficult to use on a large scale.[10] The most concerning aspect of the sequence was the final coupling step which was heterogeneous and provided a poorly defined final product with unacceptable levels of solvent impurities.[11] With the goal of addressing these issues and developing a safe and efficient manufacturing process, process development was initiated.

Synthesis of Starting Material. The first item to be addressed was supply of starting material **2**. One vendor offered **2** at a price of $5500/kg with a lead time of 16 weeks. The long lead time would have had a significant impact on the project timeline, so it was decided to prepare the material in-house.

Roche Basel has used **2** as a starting material in the synthesis of a selective *N*-methyl-D-aspartate (NMDA) receptor antagonist.[12] The reaction sequence developed by our Basel colleagues to manufacture **2** is shown in Scheme 3 and has been described in detail recently. According to the published report, the chemistry had been demonstrated in a kilo-lab then transferred to an outside manufacturer where 40 kg of **2** were generated. Prior to scaling this chemistry in the Palo Alto facility, we chose to evaluate certain aspects of the process to tailor it for our pilot plant. We envisioned a telescoped process that used one solvent and did not require the use of dioxane, a suspected carcinogen.

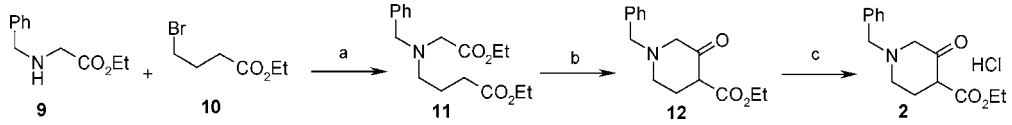
Process research revealed that **9** could be alkylated with **10** in toluene, thereby eliminating the use of dioxane. The revised procedure for the alkylation stage of the process was to combine glycine derivative **9** with 1.5 equiv of triethylamine in toluene and heat the mixture to 95 °C. Ester **10** (2 equiv) was added, and the mixture was heated at reflux until the reaction was complete. Running this stage in a reaction calorimeter showed that there was a slight exotherm during the charge of **10** (24 kJ/mol, $T_{ad} = 6.5$ °C).

A glassy residue of triethylamine hydrobromide formed during the alkylation. At temperatures above 80 °C, this glassy semisolid was difficult to filter. Lowering the temperature of the vessel to 50−60 °C resulted in a granular solid that filtered quickly.[13] Removing the triethylamine hydrobromide at an elevated temperature allowed the next stage of the process to be started almost immediately, since the Dieckmann reaction was conducted at 90−95 °C.[14]

We chose to use potassium *tert*-amylate (KTA) as the base for the Dieckmann reaction rather than use sodium ethoxide as reported by the Basel group. Potassium *tert*-amylate is commercially available as a concentrated solution in toluene (25 wt %, ca. 1.7 M), and using it removed the technical challenge of charging solid sodium ethoxide to a reactor containing hot toluene. The Dieckmann reaction was

(7) OSHA PEL: 100 ppm, Ullmann's Encyclopedia of Industrial Chemicals 2004, John Wiley and Sons: DOI: 10.1002/14356007.a08_545.
(8) TLV-TWA: 5 ppm, Ullmann's Encyclopedia of Industrial Chemicals 2004, John Wiley and Sons: DOI: 10.1002/14356007.a10_101.
(9) See ref 5.
(10) Formamidine hydrochloride is hygroscopic.
(11) See Q3C Guidelines for Residual Solvents at www.ich.org for permitted daily exposures.
(12) Scalone, M.; Waldmeier, P. *Org. Process Res. Dev.* **2003**, *7*, 418−425.
(13) Experiments in the lab have shown that using diisopropylethylamine in place of triethylamine results in a significantly faster alkylation. The reaction is complete within a few hours compared to the 12−18 h required when triethylamine was used as the scavenging base. These observations have not been tested in a pilot plant.
(14) Experiments in the lab have shown that a related salt, diisopropylethylamine hydrobromide, may be conveniently removed by adding water and separating out the aqueous layer. Although some diester **11** was extracted into the aqueous layer, using a minimal amount of water and essentially salting out the aqueous layer with the hydrobromide salt of diisopropylethylamine minimized these losses. This process improvement has not been verified on scale. If this process variant is used, then drying the toluene stock solution prior to adding base is necessary to ensure high yields in the Dieckmann reaction. The presence of water complicates the reaction by consuming KTA and facilitating hydrolysis of the ester functional groups.

Scheme 3 [a,b]



[a] Original Conditons: (a)(i) TEA, dioxane, Δ, PhMe, filter, concentrate; (b)(i) NaOEt, PhMe, (ii) HOAc, filter; (c) HCl, EtOH, concentrate. [b]Revised Conditions: (a)(i) TEA, toluene, Δ, filter; (b)(i) KTA, (ii) HOAc, H_2O; (c) HCl, EtOH, concentrate, filter.

evaluated in a reaction calorimeter and found to be moderately exothermic, with a T_{ad} of 30 °C. The exotherm associated with the reaction was easily controlled by adjusting the rate as which potassium *tert*-amylate was added to the reaction mixture.

The workup of the Dieckmann reaction was changed significantly from the published method.[12] Rather than adding a filter aid and removing the salts generated during the reaction by filtration, the reaction mixture was cooled to ca. 5 °C and neutralized with acetic acid. The acetic acid addition was only slightly exothermic (T_{ad} = 12 °C), and the internal temperature was controlled easily, even on a 20 kg scale. Water was then added to the reaction mixture, and the salts were removed by dropping the lower aqueous layer out of the reactor after an appropriate settling time. Analysis of the aqueous layer indicated a small amount of product was lost to this side stream, but the cycle time of the process was dramatically reduced by avoiding the slow filtration of a filter aid and salts.

The toluene solution of **12** was dried azeotropically and then diluted back to the predistillation volume with toluene. A solution of dry HCl in ethanol (3.5−4.0 wt %) was introduced, and the reactor contents were concentrated under vacuum to approximately two-thirds of the original volume when in-process analysis indicated that the majority of the ethanol had been removed.[15] The mixture was diluted back to its predistillation volume with heptane, and the product was collected via filtration. Hydrochloride salt **2** filtered very slowly when it was isolated from only toluene, but the filtration rate was acceptable when it was isolated from a toluene−heptane mixture.[16]

This modified procedure was demonstrated in the Palo Alto pilot plant and provided 5 and 19 kg batches of **2**.[17] With supply of starting material secured, attention was shifted to the synthesis of **1**.

Pilot Plant Campaign One. Formamidine hydrochloride was used to generate **3** from **2** in the first pilot plant campaign using reaction conditions that were almost identical to those used in medicinal chemistry. The solvent and base were switched from methanol and sodium methoxide to ethanol and sodium ethoxide. Using a slightly higher reaction temperature led to complete reaction in 6 h rather than requiring overnight. More importantly, this combination of base and solvent ensured that transesterification of **2** would not occur which would have complicated our analytical method.[18] When the reaction was deemed complete, aqueous hydrochloric acid was added to the reaction mixture and the solvent was exchanged to 2-propanol. One disadvantage of using this procedure was the coprecipitation of sodium chloride from 2-propanol. However, the product was isolated in an assay corrected yield of 88%, and the processing was straightforward.

Phosphorus oxychloride was used as a reagent and the solvent for the conversion of **3** to **4**. Although both the hydrochloride salt **3** and the sodium chloride that coprecipitated with **3** dissolved in $POCl_3$, conversion to **4** did not occur in the absence of *N*,*N*-diethylaniline. When substoiciometric amounts of *N*,*N*-diethylaniline were added to the reaction mixture, the reaction was complete within 16 h at 105 °C. However, under these conditions, unidentified polar impurities were formed and the reaction mixture was highly colored. Replacing the *N*,*N*-diethylaniline with dimethylformamide resulted in a faster reaction with fewer polar impurities and improved color characteristics. Tetramethylammonium chloride was also added to the reaction mixture and accelerated the formation of chloropyrimidine **4**. Once the reaction was deemed complete, the excess phosphorus oxychloride was removed under vacuum, the reaction mixture was coevaporated with toluene, and the residue was taken up in methylene chloride. The methylene chloride layer was worked up with aqueous potassium hydroxide and potassium phosphate,[19] and the solvent was then exchanged with 2-propanol. Morpholine was added, and the mixture was heated until the conversion of **4** to **5** was complete. An exhaustive workup followed that involved removal of the 2-propanol and replacement with water, extraction with ethyl acetate, and further water washes, followed by another solvent switch back to 2-propanol and addition of concentrated hydrochloric acid. Although the process was cumbersome, it was scalable in our facilities and generated **5** as the dihydrochloride salt in a yield of 69%.

Generation of chloroquinazolinone **7** from **8** was straightforward. Rather than using the conditions reported by discovery chemists, dioxane was replaced with tetrahydrofuran and the amount of sodium hydroxide was reduced from 13

(15) Laboratory-scale stress tests have shown that overstripping the toluene at this stage results in a lower purity of **2**. At this point, the reaction mixture was either diluted with toluene, and the distillation continued until the ethanol was removed, or diluted with heptane.

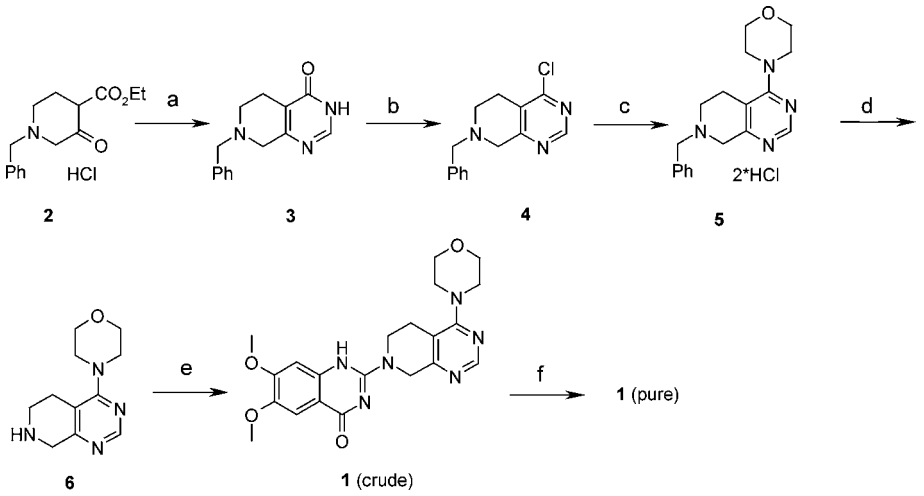
(16) The addition of heptane caused the crystals of **2** to agglomerate. Although the particle size of the crystals did not appear to increase, the agglomerated solid filtered much faster.

(17) Experiments in the lab have shown that the hydrochloride salt can be formed by adding ethanol or 2-propanol to the reaction mixture followed by the addition of chlorotrimethylsilane. This avoids having to remove the ethanol, thereby decreasing the cycle time and avoiding a distillation that is not robust to overstripping the solvent. The use of gaseous hydrogen chloride in our 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).

(18) Large-scale reactions are typically followed using HPLC. Partial generation of the methyl ester of **2** from methanol and sodium methoxide would require that both esters be identified as starting materials and be followed during the in-process analysis.

(19) Significant emulsions formed during the aqueous workup in the absence of potassium phosphate, whereas solids precipitated in the presence of only potassium phosphate.

Scheme 4[a]



[a] (a)(i) formamidine acetate, NaOEt, EtOH; (ii) NaOH, H_2O, PhMe; (iii) HOAc; (b)(i) $POCl_3$, ACN; (ii) KOH; (c) morpholine, IPA, HCl; (d) HCO_2H, $Pd(OH)_2/C$, TEA, MeOH; (e) **7**, NMP, MeOH, TEA, H_2O; (f)(i) HCl, H_2O, (ii) NH_4OH, H_2O, EtOH.

to 6 equiv. Use of this protocol eliminated the formation of the insoluble impurity reported by discovery chemistry, making this procedure a one-pot process.[20] Addition of acetic acid to the reaction mixture once the hydrolysis was complete led to precipitation of **7** in a yield of 96%. This stage of the process still suffered from low throughput, requiring approximately 30 L of solvent per kg of **8**. The cycletime of the process was also poor, which was directly related to the filter qualities of product **7**. The product was quite slow to filter on a Nutsche filter, and fines passed through the filter screen, which required the filtrate to be recirculated through the cake.

The synthetic routes to the two key intermediates (**7** and **5**) demonstrated in the first pilot plant campaign were quite similar to the routes developed in discovery chemistry. The strategy to push forward to these two intermediates with a suboptimal process was based on our assessment of the conditions used in discovery chemistry to debenzylate **5** and couple **6** with **7**. We recognized the need to modify the hydrogenation conditions, since the reaction time was too long, and our pilot plant has a limited number of reactors capable of operating at 40 psi. Adopting a process that used these conditions would limit future scale-up. The solvent used to couple **6** and **7** was not acceptable, and a method to recrystallize the API, or a stage where the reaction mixture was homogeneous, needed to be developed, since a polishing filtration was required prior to isolation of the API.

The first point was addressed by using a transfer-hydrogenation protocol to generate **6**. Lab experiments showed that substrate **5** was smoothly debenzylated within a few hours upon addition of formic acid to a mixture of methanol and triethylamine in the presence of Pearlman's catalyst. The lab protocol involved the addition of formic acid to the reaction mixture at the reflux temperature (65 °C). When these conditions were scaled to the pilot plant, vigorous off-gas was noticed, so the reaction temperature was lowered to 60 °C and maintained there until the reaction was complete. The reaction mixture was filtered over a cellulose filter aid to remove the catalyst and added to a mixture of **7** in methanol, triethylamine, and *N*-methylpyrolodinone. The reaction mixture was partially concentrated and then heated at reflux (ca. 65 °C) for 24 h, when in-process monitoring showed the coupling to be complete. The reactor contents were concentrated at atmospheric pressure while the internal temperature was raised to ca. 90 °C. Water was then added, and the internal temperature was adjusted to ca. 22 °C over a 4 h period prior to collecting the product on a filter. The first pilot plant campaign generated 2.5 kg of crude **1** with a HPLC area-normalized purity of 97.1%. The crude product contained **7** (1.6%) and quinazolindione **13** (1.2%). The dense solid isolated from this process was anhydrous and highly crystalline and was not solvated.

At this stage, all that remained was to upgrade the purity of the API and have a polishing filtration in the final isolation procedure. The solubility of **1** in organic solvents was judged to be too low to make a recrystallization practical, especially as the scale increased. The process that was ultimately scaled involved suspending crude **1** in water and the addition of concentrated hydrochloric acid. The dihydrochloride salt of **1** was found to be very soluble in water and dissolved in 6 L of water per kg of **1**. This solution was then passed through a 1 μm filter and transferred to a reactor verified to be free of foreign particulate which contained ammonium hydroxide and ethanol. The ammonium hydroxide neutralized the hydrogen chloride, and the free base of **1** precipitated with an excellent recovery (95%) and purity (99.5% by area-normalized HPLC).

Pilot Plant Campaign Two. As the project moved forward, it became clear that more material would be required to complete the preclinical studies and prepare for entry into humans. The process was revisited, and observations made during the first pilot plant campaign were addressed. The process demonstrated in the second pilot plant campaign is shown in Scheme 4.

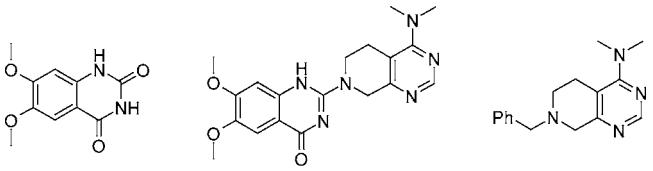
(20) The insoluble impurity was quinazolindione **13**, which was the result of overhydrolysis of **7**. It is unknown if the generation of this impurity is solvent related, but it is suspected that its generation was related to the large excess of base used by discovery chemists.

Formamidine hydrochloride was not the reagent of choice in the formation of **3**. Formamidine hydrochloride is not readily available on a large scale and is rather costly. Contacted vendors quoted prices of $1000−2250/kg with lead times of 3−4 months. Formamidine hydrochloride is quite hygroscopic, a characteristic that makes it difficult to handle on a large scale and complicates long-term storage. We also wanted to change the workup of the process used to generate **3** and eliminate the high salt load of the isolated product.

Formamidine acetate was demonstrated as a replacement for formamidine hydrochloride. In addition to being nonhygroscopic, it is readily available and more economical.[21] Consistently better yields were obtained if formamidine acetate, **2**, and sodium ethoxide were combined in ethanol prior to adjusting the reaction mixture to reflux rather than adding the base at the reflux temperature. Although there was some reluctance to charging all of the reactants to a reactor and then heating, the exotherm observed upon addition of the sodium ethoxide solution was quite mild and was the result of neutralizing the hydrogen chloride and acetic acid. Since these neutralizations occurred prior to heating the reaction mass, the process still had an addition-controlled exotherm. The process that was demonstrated in the pilot plant involved combining formamidine acetate (1.5 equiv), **2**, and sodium ethoxide (3.5 equiv) in ethanol and adjusting the reaction mass to reflux until the reaction was complete.

Isolation of the free base **3** was accomplished by exchanging the solvent from ethanol to toluene upon completion of the reaction. Toluene was added as the ethanol was distilled, and when the ethanol content of the pot dropped below four percent by weight, as monitored by in-process NMR analysis, water and sodium hydroxide were added. The addition of aqueous base formed the sodium salt of **3**, which was extracted into the aqueous phase. The free base of **3** was precipitated by adding acetic acid to the separated aqueous layer. Yields for this stage approached 85% in the lab, and product purity was greater than 98% (area normalized HPLC). This chemistry was demonstrated in the pilot plant using 22 kg of **2** and generated 14 kg of **3**. The product was filtered on an agitated filter dryer, since **3** displayed a tendency to contract away from the walls of the filter once the filtrate passed through the cake. Using an agitated filter dryer allowed the cake to be smoothed prior to washing, leading to more efficient washes. The only downside of using this filter rather than a Nutsche filter was the increased amount of product lost as heel. The higher losses resulted in a slightly lower yield during the demonstration run in the pilot plant. The product was isolated in 79% yield and excellent purity (>99%) as judged by area-normalized HPLC.

Using **3** as the free base led to some downstream process improvements. First and foremost, the amount of phosphorus oxychloride required for the transformation to **4** was reduced. Instead of using it as a solvent, it was now possible to conduct the chlorination in acetonitrile with 1.7 equiv of phosphorus oxychloride. A small exotherm had been noted in the lab when phosphorus oxychloride was charged to the mixture of **3** and acetonitrile. To have an addition-controlled exotherm and minimize accumulation of phosphorus oxychloride, the addition of phosphorus oxychloride was done at 50−55 °C. The reaction between **3** and phosphorus oxychloride was very clean, showing an essentially peak to peak transformation when monitored by HPLC. Unlike the process demonstrated in the first pilot plant campaign, this process did not require DMF to catalyze the reaction. Removing DMF from the reaction not only removed the possibility of generating dimethylcarbamyl chloride,[22] but it was also expected to remove one of the potential impurities from the API. When the product of the first pilot plant batch was analyzed, one of the impurities had a mass consistent with **14**. Presumably this was generated from **15** and carried forward to the final product.



13 **14** **15**

Using a water miscible solvent for the chlorination stage allowed an in situ quench to be developed. Although initial attempts to add sodium hydroxide to the reaction mixture were not promising due to the precipitation of sodium phosphate, potassium hydroxide functioned very well and solids did not precipitate from the reaction mixture. The neutralization was quite exothermic, and an assessment of the reaction and quench was conducted with a reaction calorimeter, which is discussed in detail later.

Morpholine was added to the reaction, and the mixture was heated until the coupling to form **5** was complete. Water and methyl *tert*-butyl ether (MTBE) were added, and the product was extracted into the MTBE layer. A second extraction of the aqueous layer with MTBE was necessary to increase the recovery of **5**. The solvent was then exchanged to 2-propanol, and the dihydrochloride salt of **5** was formed upon addition of concentrated hydrochloric acid. This process was demonstrated in the pilot plant using 14 kg of **3** and produced 17.9 kg of **5**, which was isolated as the dihydrochloride salt in acceptable yield (80%) and excellent purity (99.9% by area normalized HPLC).

The throughput issue in the preparation of **7** was resolved by using potassium hydroxide in place of sodium hydroxide. The potassium salt of **7** was much more soluble in the THF−water mixture than the corresponding sodium salt. When sodium hydroxide was used as the base, the hydrolysis required approximately 8 and 22 L of THF and water, respectively, per kg of **8**. The solvent requirements dropped to 5 L/kg of THF and 9 L/kg of water when potassium hydroxide was used as the base. Although much better reactor throughput was achieved with this reduction in solvent requirement, the filterability of **7** remained an issue. Several acid/solvent combinations were examined without any improvement in filtration rate. Finally, it was decided to filter

(21) Degussa offers formamidine acetate in 80 kg drums at $30/kg.

(22) Levin, D. *Org. Process Res. Dev.* **1997**, *1*, 182.

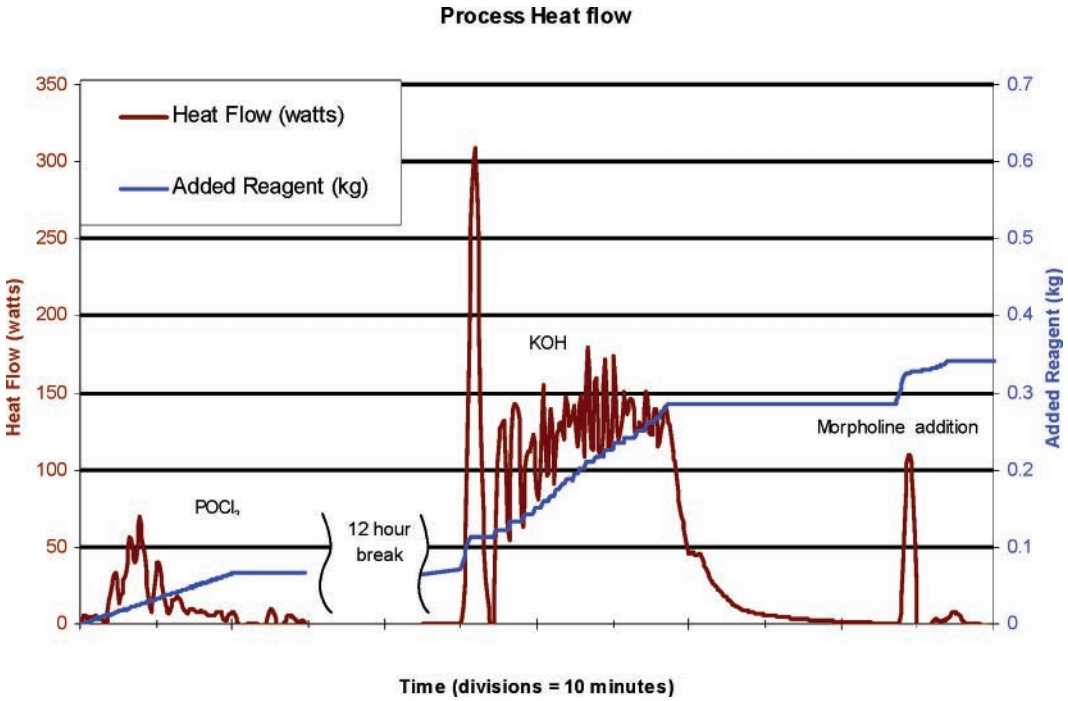


Figure 1. **RC1 heat flow for conversion of 3 to 5.**

7 on a centrifuge in the pilot plant, which improved the cycle time by reducing the time required for the filtration. The demonstration batch was conducted on 10 kg of **8** and afforded **7** in a 97% yield.

The last stage of the process did not differ significantly from the conditions used in the first pilot plant campaign. A minor change was made in the debenzylation stage of the process. Prior to addition of formic acid, the reaction mixture was adjusted to 55−65 °C. The generated off-gas was then easily controlled using these conditions. The workup and coupling with **7** were done as in the first pilot plant campaign. The final stages of the process were started with 15.4 kg of **5** (as the dihydrochloride salt) and 8.7 kg of **7**. This combination produced 13.7 kg of **1** with a purity of 99.6% (area normalized HPLC).

The final isolation protocol was identical to that demonstrated in the first campaign. The recovery of product was 89%, and the only impurities, which were detected in the filtrate, were **6** and **13**. The impurity present in the first batch and presumed to be **14** was not detected in material isolated from the second pilot plant campaign. Removal of the dimethylformamide as an activator for the phosphorus oxychloride coincided with the removal of this impurity from the API.

Reaction Calorimeter Investigation: Synthesis of 5 from 3. While developing the telescoped process to generate **5** from **3**, it was noted that each of the three steps in the process was exothermic. The addition of phosphorus oxychloride to **3** was mildly exothermic, as was the addition of morpholine. The concern for scale-up was the quench with potassium hydroxide that followed the phosphorus oxychloride reaction. To obtain a better understanding of the heat flow of the process and determine the magnitude of the expected exotherms, the process of generating **5** from **3** was examined using a reaction calorimeter. The heat output for the chlorination, quench, and morpholine coupling is shown in Figure 1.

Acetonitrile and **3** (60 g) were combined in a Mettler RC1, and the reactor was heated to 65 °C. Phosphorus oxychloride (65 g, 1.7 equiv) was added over 20 min while the temperature was maintained at 65 °C. The exotherm started immediately upon addition of phosphorus oxychloride and subsided after 1 equiv was added. On the basis of heat output, the reaction was complete at this point. However, in-process monitoring showed that the overall transformation was not complete. Lab experiments conducted prior to the RC-1 experiment indicated that a reduction in the phosphorus oxychloride charge was accompanied by a longer reaction time. To have a shorter reaction time, excess phosphorus oxychloride was used. The total energy given off during the reaction of **3** with phosphorus oxychloride was 19 kJ, which corresponded to an adiabatic temperature rise of 8 °C.

When the chlorination was deemed complete, the reactor contents were cooled to 22 °C, and concentrated potassium hydroxide (216 g of 50% by weight solution) was added over 30 min. A large exotherm was observed which started immediately upon addition of potassium hydroxide and continued throughout the dosing of base. The total energy released during the potassium hydroxide addition was 223 kJ (T_{ad} = 141 °C). Due to the large adiabatic temperature rise, the potassium hydroxide used in the pilot plant was divided into multiple portions and each was added to the reactor slowly. In this way, if control of the addition rate was lost, the entire amount of potassium hydroxide would not be added at one time.

Morpholine (45 g, 2.1 equiv) was charged to the reactor once the chlorination stage was quenched. Consistent with the observations in the lab, this addition had a small exotherm, with a total heat output of 4 kJ (T_{ad} = 9 °C).

Conclusion

A process to generate RO3203546 was developed and demonstrated in two pilot plant campaigns. In the first pilot plant campaign, a debenzylation process was developed that used transfer hydrogenation rather than a medium pressure hydrogenation. Eliminating the need for the specialized equipment required to safely perform hydrogenations on a large scale made the process more amenable to further scale-up. Replacing dioxane and methoxyethanol with solvents that are more acceptable in the pharmaceutical industry was also a significant achievement. Most importantly, a highly crystalline, nonsolvated form of the API was discovered, and a method to purify the compound and ensure that extraneous material was removed from the drug substance was demonstrated.

The second pilot plant campaign integrated enhancements in the early stages of the process. Pyrimidinone **3** was generated with formamidine acetate and isolated as a free base. Generation of **3** as a free base simplified the analytics, since **3** did not need to be assayed for sodium chloride content. Free base **3** reacted more smoothly in the chlorination sequence with $POCl_3$ than did the hydrochloride salt. The charge of $POCl_3$ was greatly reduced, and an in situ quench with KOH was developed. Although the quench was very exothermic, evaluation with a reaction calorimeter showed that the reaction was instantaneous and could be safely scaled as long as control of the addition rate of KOH was maintained. The quenched reaction mixture was coupled directly with morpholine and led to the production of **5** with excellent throughput and an acceptable cycle time.

Processes that led to required reagents **2** and **7** were also demonstrated on-scale. Modification of a published procedure allowed **2** to be generated in-house which dramatically accelerated the development of RO3202546. Although the modifications made to the synthesis of **2** resulted in a slightly lower yield than that reported in the literature, the cycle time of the process was improved. Since the goal of the in-house synthesis was to generate material within weeks rather than wait months for an outside vendor, the marginally lower yield was acceptable.

Experimental Section

General: All reactions were conducted in glass-lined reactors under a nitrogen atmosphere. All equipment and lines were checked for leaks by pressuring the system with nitrogen prior to use.

Ethyl *N*-Benzyl-3-oxo-piperidine-4-carboxylate Hydrochloride (2): *N*-Benzylglycine ethyl ester (15.9 kg, 82.8 mol, 1.0 equiv), triethylamine (15.2 kg, 126.5 mol, 1.5 equiv), and toluene (110 kg) were combined and heated to 95 °C. Ethyl 4-bromobutyrate (31.2 kg, 155.8 mol, 1.9 equiv) was added over 10 min, and the reaction mixture was adjusted to reflux. After 5 h, in-process analysis indicated that the reaction was complete (<1% starting material by area normalized GC). The reaction mixture was cooled to 50 °C and filtered. The reaction vessel and filter were rinsed with toluene (22 kg), and the combined filtrate was transferred to another reactor. The reactor contents were adjusted to ca. 90 °C, and potassium *tert*-amylate (25% solution in toluene, 76.9 kg, 150.5 mol, 1.8 equiv) was added. The resulting mixture was heated at 90−100 °C until in-process analysis (GC) showed the absence of starting glycine ester (3.5 h). The reactor contents were cooled to ca. 5 °C, and acetic acid (9 kg, 151.9 mol, 1.8 equiv) was added over 10 min while the temperature was maintained below 10 °C. Water (70 kg) was added, and the resulting mixture stirred for 45 min. The reactor contents were allowed to settle, and the lower aqueous layer was removed. The organic layer was concentrated under vacuum to ca. 100 L. Vacuum was released on the reactor, and toluene (140 kg) was added to the concentrate. A solution of HCl (3.1 kg, 114 mol, 1.4 equiv) in ethanol (88 kg) was added, and the resulting mixture was stirred at ca. 22 °C for 30 min. The reactor contents were concentrated using an isolated vacuum source equipped with a caustic scrubber to a volume of ca. 200 L. Heptane (130 kg) was added, and the temperature was adjusted to 22 °C. The mixture was left overnight with slow stirring. The reactor contents were cooled to ca. 5 °C, and after 1 h, the slurry was filtered and rinsed with heptane (74 kg). The solid was dried on the filter until in-process analysis showed the loss on drying to be less than 1%. Total product discharged from the filter: 18.8 kg (76.8% yield). Mass spectrum: m/z 262 (M^++1); wt % chloride calcd, 11.91%; found, 11.76%; mp 162−165 °C.

7-Benzyl-5,6,7,8-tetrahydro-3*H*-pyrido[3,4-*d*]pyrimidin-4-one (3): Formamidine acetate (11.4 kg, 10 mol, 1.5 equiv), keto-ester **2** (22.0 kg, 73.9 mol, 1.0 equiv), ethanol (55 kg), and sodium ethoxide (84 kg, 21 wt % in ethanol, 297 mol, 3.5 equiv) were combined, and the mixture was adjusted to reflux. After 2.5 h, in-process analysis indicated the reaction was complete. Toluene (97 kg) was added, and the mixture was concentrated under vacuum from an initial volume of ca. 310 L to a final volume of ca. 150 L. Toluene was added as necessary to maintain a reactor volume of ca. 150 L, and the distillation continued until in-process analysis (NMR) indicated that the majority of the ethanol was removed. Vacuum was released from the system, water (125 L) was added, and the contents were adjusted to <30 °C. Sodium hydroxide (4.4 kg, 50% solution in water, 36.3 mol, 0.7 equiv) was charged, and the lines were rinsed forward to the reactor with ca. 7 kg of water. The biphasic mixture was stirred for ca. 1.5 h. The layers were separated glacial acetic acid was added to aqueous layer until the pH was 7. The reactor contents were adjusted to 85−95 °C and allowed to stir at this temperature for 1−2 h, then cooled to 5−10 °C and stirred for 1−2 h. The product was filtered, [23] rinsed with water (ca. 34 L), then dried. Yield: 14.0 kg of **3**, purity 100% (area normalized HPLC), water content 0.3% (Karl-Fisher method). Mass spectrum: m/z = 242 (M^++1), mp: 195−197 °C.

7-Benzyl-4-morpholin-4-yl-5,6,7,8-tetrahydro-pyrido-[3,4-d]pyrimidine (5): Pyrimidinone **3** (14.0 kg, 5.8 mol, 1 equiv) and acetonitrile (77 kg) were combined and heated to 50−60 °C. Phosphorus oxychloride (15 kg, 9.8 mol, 1.7 equiv) was charged over 15 min, and the reaction mixture was adjusted to ca. 80 °C. The reaction mixture was kept at

(23) An agitated filter dryer was used for this filtration because the cake will pull away from the walls of the filter.

this temperature until starting material was consumed (ca. 4 h). The reaction mixture was then cooled to below 20 °C, and potassium hydroxide (51 kg of 50% aqueous solution, 45 mol, 7.7 equiv) was added (Caution: exothermic reaction) while the temperature of the reactor contents was kept below 25 °C.[24] Morpholine (10.5 kg, 12.0 mol, 2.1 equiv) was charged to the reactor, and the lines were rinsed with ca. 5 kg of acetonitrile. The reactor contents were adjusted to ca. 80 °C, and the contents stirred at this temperature for 4 h after which time in-process analysis indicated that pyrimidine intermediate **4** was consumed (<0.5% AN HPLC). The temperature was adjusted to ca. 22 °C, and water (140 L) and MTBE (50 kg) were added. After a mixing time, the layers were separated and the aqueous layer was re-extracted with MTBE (50 kg). The combined organic layers were concentrated,[25] and the solvent was switched to 2-propanol. The final volume was adjusted to ca. 100 L, and concentrated hydrochloric acid (12.1 kg, 12.2 mol, 2.1 equiv) was added. The slurry that formed was cooled to 5−10 °C, stirred at this temperature for ca. 2 h, and filtered and rinsed with cold (5−10 °C) 2-propanol (ca. 14 kg). The product was dried under vacuum at ambient temperature and discharged to afford 17.86 kg of **5** as the dihydrochloride salt (80.3% yield) having a purity of 99.9% (AN HPLC) and contained 4.6% water (KF method). Mass spectrum: $m/z = 311$ (M^++1); mp 226−232 °C.

2-Chloro-6,7-dimethoxy-3*H*-quinazolin-4-one (7): Potassium hydroxide (15 kg, 50% solution, 134 mol, 3.5 equiv) was added to a mixture of 2,4-dichloro-6,7-dimethoxyquinazoline (10 kg, 38.6 mol, 1 equiv), tetrahydrofuran (45 kg), and water (80 L). The mixture was stirred overnight (ca. 15 h) at ca. 22 °C. Glacial acetic acid (7.5 kg, 125 mol, 3.2 equiv) was added, and the product that precipitated was filtered on a centrifuge,[26] washed with water, and dried at 55 °C under vacuum to an essentially constant weight. The total amount of dry product was 8.94 kg (96.5% yield) having a purity of 99.4% AN HPLC. Mass spectrum: $m/z = 241$ (M^++1). Anal. Calcd. For $C_{10}H_9ClN_2O_3$: C, 49.91; H, 3.77; N, 11.64. Found: C, 50.35; H, 3.85; N, 11.52. Mp 270−272 °C (lit.[27] 270−272 °C).

6,7-Dimethoxy-2-(4-morpholin-4-yl-5,8-dihydro-6*H*-pyrido[3,4-*d*]pyrimidin-7-yl)-1*H*-quinazolin-4-one (1) (Crude): A 400 L glass-lined reactor which was connected to a hydrogen vent panel and flame arrestor was charged with Pearlman's catalyst (1 kg), **5** (15.4 kg, 39.3 mol, 1 equiv), methanol (100 kg), and triethylamine (18.2 kg, 178 mol, 4.6 equiv). The temperature of the reactor contents was adjusted to 55−65 °C, and formic acid (5 kg, 105 mol, 2.7 equiv) was added via a metering pump. The reactor contents were stirred at 60−65 °C until in-process analysis indicated less than 1% of **5** remained in the mixture (6 h). The mixture was cooled to ca. 22 °C, and the reactor was purged with nitrogen several times to ensure hydrogen removal. The catalyst was removed by passing the reaction mixture through a cartridge filter, and the reactor was rinsed forward with methanol (2 × 30 kg). The filtrate was transferred directly to another 400 L reactor that contained a solution of **7** (8.8 kg, 36.5 mol, 0.9 equiv), NMP (34 kg), methanol (67 kg), and triethylamine (12.2 kg, 121 mol, 3.1 equiv) at 50 °C.[28] The reactor was set up for atmospheric distillation, and the reactor contents were concentrated to a final volume of ∼110 L (pot temperature 80−85 °C). Water (200 L) was added, and the distillation continued until the pot volume was ca. 200 L. The reactor contents were cooled to 22 °C over 6 h and then stirred at 22 °C for ca. 10 h. The slurry was filtered, rinsed with water (ca. 50 L) and ethanol (ca. 30 kg), and then dried under vacuum. Total yield of product was 13.65 kg (89.3% yield) having a purity of 99.6% (AN HPLC).

6,7-Dimethoxy-2-(4-morpholin-4-yl-5,8-dihydro-6*H*-pyrido[3,4-*d*]pyrimidin-7-yl)-1*H*-quinazolin-4-one (1) (Pure): Crude **1** (13.6 kg, 31.8 mol, 1 equiv), water (95 kg), and concentrated hydrochloric acid (6.8 kg, 68.5 mol, 2.2 equiv) were combined and stirred at 20−25 °C until the solids dissolved. The mixture was transferred through a polishing filter to a reactor[29] that contained ammonium hydroxide (8.6 kg, 69 mol, 2.2 equiv), water (90 kg), and ethanol (150 kg). The slurry that formed was filtered, washed with ethanol (30 kg), and dried under vacuum. The filter was discharged to afford pure **1** (12.1 kg, 89% yield) as a white powder, in a purity of 99.9% (AN HPLC). Mass spectrum: $m/z = 425$ (M^++1). Anal. Calcd. For $C_{21}H_{24}N_6O_4$: C, 59.42; H, 5.70; N, 19.80. Found: C, 58.61; H, 5.63; N, 19.45. Mp 285−287 °C.

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(24) On this scale, the addition of potassium hydroxide required 2.5 h.
(25) The organic solutions were transferred as room allowed to the 200 L reactor, leaving a headspace for solvent distillation.
(26) The particle size of the precipitate is quite small, and the filtration is slow on Nutsche type filters.
(27) Hess, H.-J.; Cronin, T. H.; Scriabine, A. *J. Med. Chem.* **1968**, *11*, 130−136.
(28) This mixture was heated at ca. 50 °C until the solids dissolved (ca. 1 h).
(29) This reactor had been previously verified to be free of particulate. All liquid streams entering this system entered via a polishing filter.