Organic Process Research & Development **2006**, *10,* 391–397

Full Papers

Concise Synthesis of a Selective α_1-Adrenoceptor Antagonist

Terrence J. Connolly,* Michael Matchett, Patrick McGarry, Sunil Sukhtankar, and Jiang Zhu

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

Abstract:

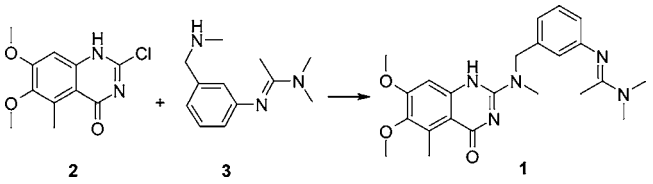
An efficient synthesis of an adrenoceptor antagonist has been developed and demonstrated in a pilot plant. A linear synthesis that relied on a catalytic reduction of a rather insoluble nitroaromatic proved to be a viable route. The active pharmaceutical ingredient (API) that contained an amidine functional group was generated from the amino-containing precursor by activation of dimethylacetamide (DMA) with phosphorus oxychloride ($POCl_3$). The reaction between DMA and $POCl_3$ was studied using ReactIR and was found to be a fast but not instantaneous reaction. The iminium salt generated from DMA and $POCl_3$ had acceptable stability to allow for its use on a pilot-plant scale; however, a trend towards decomposition was revealed on the basis of in situ FTIR data. Formation of the complex was evaluated in a reaction calorimeter (RC-1), and the stability of the complex was probed with an Advanced Reactive System Screening Tool (ARSST).

Introduction

Benign prostatic hyperplasia (BPH) is a male urological disorder characterized anatomically by enlargement of the prostate gland due to cellular proliferation of prostatic tissue. The symptoms of BPH can be classified as obstructive (hesitancy, low flow, high residual volume) or irritative (frequency, urgency, nocturia, reduced bladder capacity). Clinical studies have shown α-1 adrenoceptor antagonists to be effective in relieving both the obstructive and irritative symptoms associated with BPH.[1−3] Although subtypes of the α-1 adrenergic receptors are known (α_{1A}, α_{1B}, and α_{1D}),[4] the alpha-1 blockers used to treat BPH currently are nonsubtype selective and have the potential to cause cardiovascular side effects such as postural hypotension and dizziness. Clinical doses can be titrated against the side effects although efficacy may be sacrificed.

Efforts at Roche Palo Alto to develop new chemical entities (NCE) for treating irritative and obstructive BPH symptoms included antagonists displaying selectivity for α_{1A} and α_{1B} adrenoceptor subtypes.[5−7] Compound **1** was recently selected as a potential clinical candidate, and larger quantities of **1** were required to support preclinical studies.

Scheme 1



Results and Discussion

The key step in the discovery synthesis is shown in Scheme 1. This route relied on generating two late-stage intermediates and coupling them in the final step to generate **1**. Although this approach allowed for significant flexibility during the discovery process, it was not suitable for the preparation of large amounts of **1** due to the synthesis and physical properties of **3** (Scheme 2).

The synthesis of **3** required several steps to assemble the amidine functional group in the presence of the benzylic amine. The sequence started with **4** and involved sequential protection of the amine with *tert*-butylcarbonyl anhydride, catalytic hydrogenation of the nitro group, condensation with dimethylacetamide dimethylacetal (DMADMA), and removal of the nitrogen protecting group. The absence of crystalline or solid intermediates in the sequence used to prepare **3** would require telescoping the API synthesis from **4** to **1**. This route was not viewed as having any potential for a large-scale synthesis. The expected result of such extensive processing was a final product of unacceptable quality.

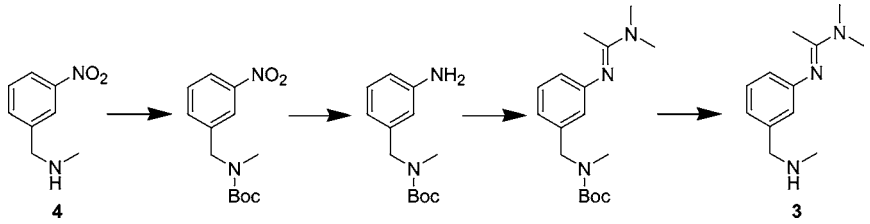
Once **1** was identified as a clinical candidate, a diversity-driven synthesis was no longer important, and an efficient route to **1** was essential. Regardless of the route to **1**, a method to prepare **2** was required and is shown in Scheme 3. Quinazolinedione **5**[8] was converted to the dichloride **6**

* Correspondence should be addressed to this author at current address: Department of Process Chemistry, Celera, 180 Kimball Way, South San Francisco, CA, 94080, U.S.A. E-mail: t_con2002@yahoo.com.

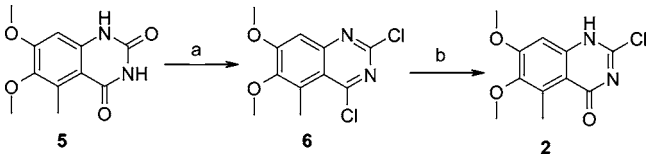
(1) Djavan, B.; Marberger, M. *Eur. Urol.* **1999**, *36*, 1−13.
(2) Kumar, V. L.; Dewan, S. *Int. Urol. Nephrol.* **2000**, *32*, 67−71.
(3) Michelotti, G. A.; Price, D. T.; Schwinn, D. H. *Pharmacol Ther.* **2000**, *88*, 281−309.
(4) Hieble, J. P.; Bylund, D.; Clarke, D. E.; Eikenburg, D. C.; Langer, S. Z.; Lefkowitz, R. J.; Minneman, K. P.; Ruffolo, R. R. *Pharmacol. Rev.* **1995**, *47*, 267−270.
(5) Becker, C. K.; Caroon, J. M.; Melville, C. R.; Padilla, F.; Pfister, J. R.; Zhang, X. WO 02/053558, 2005.
(6) Chin, E.; Cournoyer, R. L.; Keitz, P. F.; Lee, E. K.; Lopez-Apia, F. J.; Melville, C. R.; Padilla, F.; Weinhardt, K. K. WO 2005005397, 2005.
(7) Connolly, T. J.; Keitz, P. F.; Lee, E. K.; Li, J.; Lopez-Apia, F. J.; McGarry, P. F.; Melville, C. R.; Nitzan, D.; O'Yang, C.; Padilla, F.; Weinhardt, K. K. WO 2005005395, 2005.
(8) Connolly, T. J.; McGarry, P.; Sukhtankar, S. *Green Chem.* **2005**, *7*, 586−589 2005.

10.1021/op050122h CCC: $33.50 © 2006 American Chemical Society
Published on Web 05/04/2006

Scheme 2



Scheme 3[a]



[a] Reagents and conditions: a) $POCl_3$, ACN, H_2O; b) KOH, THF, HOAc.

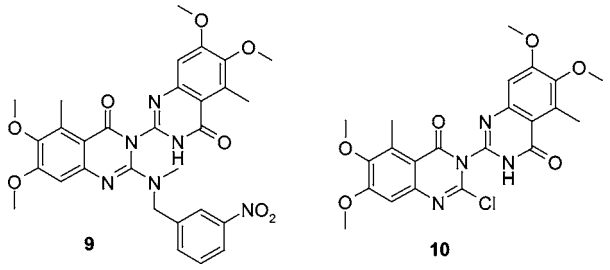


Figure 1.

with phosphorus oxychloride (4 equiv) in acetonitrile. The reaction required 24 h to go to completion, even when conducted at reflux in acetonitrile. The reaction mixture was quenched into water, and the product precipitated in a loss-on-drying (LOD)-corrected yield of 87%.[9] Water-wet **6** was hydrolyzed with KOH in THF using conditions described previously for a related compound,[10] and chloroquinazolinone **2** was generated in near quantitative yield with a purity of 97% by area normalized HPLC (AN HPLC) analysis.

The most direct route from **2** to **1** appeared to be through coupling of **2** and **4**, followed by reduction of the nitro group and conversion to the amidine (Scheme 4). Coupling of **2** and **4** (1.15 equiv as the hydrochloride salt)[11] occurred readily in 2-propanol in the presence of diisopropylethylamine (2.5 equiv). The reaction was performed in 12 volumes (L/kg of **2**) of 2-propanol and was complete within a few hours under reflux. The mixture remained heterogeneous throughout the reaction. When the coupling was complete, water (3 L/kg of **2**) was added to dissolve diisopropylethylamine hydrochloride. Addition of water while the reaction mixture was at reflux followed by a gradual cooling period rather than cooling the mixture and adding water led to better filtration rates of **7**. Product **7** was isolated in 94% yield with a purity of 97%, and entrainment of diisopropylethylamine hydrochloride in the product cake was not observed.[12] The only impurity detected had a molecular mass consistent with structure **9** (see Figure 1) which could have resulted from further reaction of the product (**7**) with **2**. Alternatively, **9** could have formed from **10**, which may have formed during the preparation of **2**.[13]

The low solubility of **7** in 2-propanol/water was a factor in achieving a high yield in the coupling stage. However, it was soon discovered that **7** had limited solubility in many solvents, which complicated the development of a catalytic hydrogenation sequence. Adding base to the alcohol/water mixtures used as solvents did not increase the solubility of **7** through ionization. Transfer hydrogenation[14] was briefly explored, and the initial results were promising. Compound **7** was reduced to **8** in ethanol/water in the presence of palladium on carbon, triethylamine, and formic acid. Product **8** was not completely soluble in the reaction mixture but could be dissolved by lowering the pH to 1−2 with HCl when the reduction was complete. The heterogeneous catalyst was removed by filtration, and product **8** was precipitated from the filtrate by adding sodium hydroxide until the pH was neutral. As the reaction was scaled up, the extreme heterogeneous nature[15] of the reaction mixture caused pH fluctuations that impacted the extent of reduction. Although addition of more formic acid and base eventually caused complete conversion to **8**, salts sometimes precipitated with product **8**. The unpredictable nature of the reaction and inconsistent quality of the penultimate product were viewed as process liabilities, and this route was not developed further.

Eventually, standard catalytic hydrogenation conditions were developed using a rather unconventional solvent system of THF (10 L/kg of **7**), methanol (5 L/kg of **7**), and aqueous NaOH (1 equiv). Under these conditions, **7** dissolved completely and was smoothly reduced with hydrogen and a palladium on carbon catalyst. Hydrogenolysis of the product was not observed, even under grossly extended reaction times. When the reduction was complete, the catalyst was removed by filtration, and the THF was replaced with methanol. Water was added, and **8** was precipitated by adjusting the pH to 5−6 with acetic acid. Precipitation of **8** from methanol/water at 50−55 °C resulted in a product with superior filtration characteristics. The reduction was complete

(9) Eleven kilograms of product with an LOD of 38% was isolated. Drying trials indicated that decomposition of the product would occur when the water-wet cake was dried at elevated temperatures.

(10) Connolly, T. J.; Matchett, M.; Sarma, K. *Org. Process Res. Dev.* **2005**, *9*, 80−87.

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

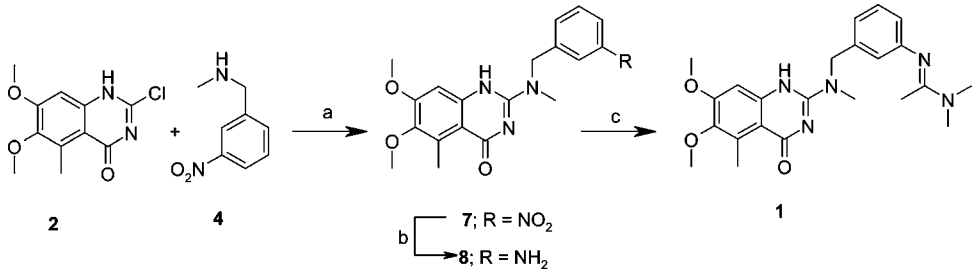
(12) When triethylamine was employed as the base in the coupling reaction of **2** and **4** and the same reaction conditions were used, the product cake did contain triethylamine hydrochloride. Increasing the water charge was not examined since throughput was already starting to suffer at 15 L/kg **4**.

(13) The presence of **10** in **2** was not verified.

(14) Johnstone, R. A. W.; Wilby, A. H.; Entwistle, I. D. *Chem. Rev.* **1985**, *85*, 129−170.

(15) Although all hydrogenations involving a metal catalyst on an insoluble support are heterogeneous, this mixture was termed "extreme" because neither the starting material nor the product was entirely soluble in the reaction mixture. The reduction process involved partial solubility of the starting material and precipitation of the product.

Scheme 4[a]



[a] Reagents and conditions: a) DIPEA, IPA, H_2O; b) H_2, Pd/C, NaOH, MeOH, THF, HOAc; c)$POCl_3$, DMA, ACN, DCM, IPA.

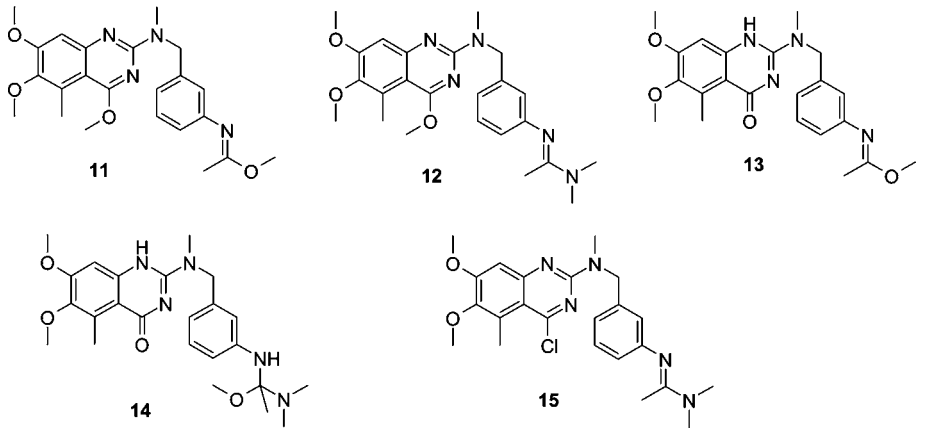


Figure 2.

within 2−3 h, and **8** was isolated in 90% yield on a 0.5 kg scale and 96% on a 5.1 kg scale. In both cases, product purity was excellent (>99%) as judged by AN HPLC.

Several conditions to install the amidine functional group were investigated. Heating **8** in alcohol or ether solvents with DMADMA (5 equiv) was investigated and gave less than ideal results. In addition to forming the desired product **1**, impurities **11**, **12**, and **13** were formed (Figure 2). Compounds **11** and **12** were generated through O-methylation by DMADMA whereas **13** was formed via an alternative reaction pathway from intermediate **14**.[16] O-Methylation presumably occurred through base-mediated tautomization of the quinazolinone moiety that resulted from the presence of DMADMA.

We next examined Dossena's conditions, who has shown that the amidine functional group can be installed through activation of dimethylacetamide (DMA) with trifluoromethansulfonic anhydride (Tf_2O).[17] When Tf_2O was added to a methylene chloride solution of DMA and the resulting mixture was added to **8** in methylene chloride, **1** was the only product formed and was isolated in 98% yield.

The relatively high cost of Tf_2O led us to consider other activating agents, and phosphorus oxychloride ($POCl_3$) was found to be an effective replacement.[18] Formation of the iminium salt from DMA with $POCl_3$ seemed to be solvent dependent, and results were a little more variable than when

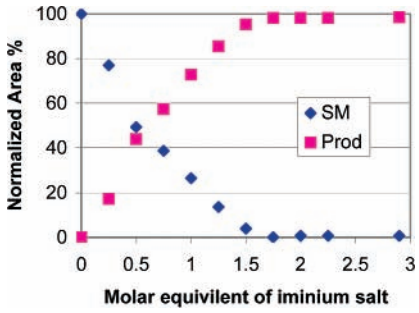


Figure 3. **Conversion of 8 to 1 with $POCl_3$−DMA complex.**

Tf_2O was used. However, activation of DMA appeared to be fast in acetonitrile and the resulting complex appeared to be relatively stable. Parameter-ranging experiments demonstrated that the reaction required only slightly more than 1.5 equiv of the iminium salt to consume all of the starting material (Figure 3). However, when the complex (1.5 equiv) was aged at room temperature for 48 h prior to adding **8**, 11% starting material remained, indicating complex instability. Repeating this experiment with 2.5 equiv of the complex led to complete conversion of **8** to **1**. Reaction stress tests with 2.5 equiv of the complex indicated that the process would be robust to long addition and reaction times, and the only byproduct formed was **15** (See Figure 2). Extending the reaction time to 5 h led to 2% (AN HPLC) of **15**, and after 5 days at ambient temperature, only 4% (AN HPLC) of **15** was formed. When the reaction was complete, it was quenched by addition of water and NaOH and by separation

(16) Interestingly, compound **13** decomposed to **8** in the presence of TFA. Initial analysis by HPLC that used TFA to modify the mobile phase seemed to indicate that the forward reaction had stalled. Analysis of the reaction by TLC indicated the absence of starting material and the presence of a nonpolar impurity, later identified as **13**.

(17) Sforza, S.; Dossena, A.; Corradini, R.; Virgili, E.; Marchelli, R. *Tetrahedron Lett.* **1998**, *39*, 711−714.

(18) Bredereck, H.; Gompper, R.; Klemm, K.; Rempfer, H. *Chem. Ber.* **1959**, *92*, 837.

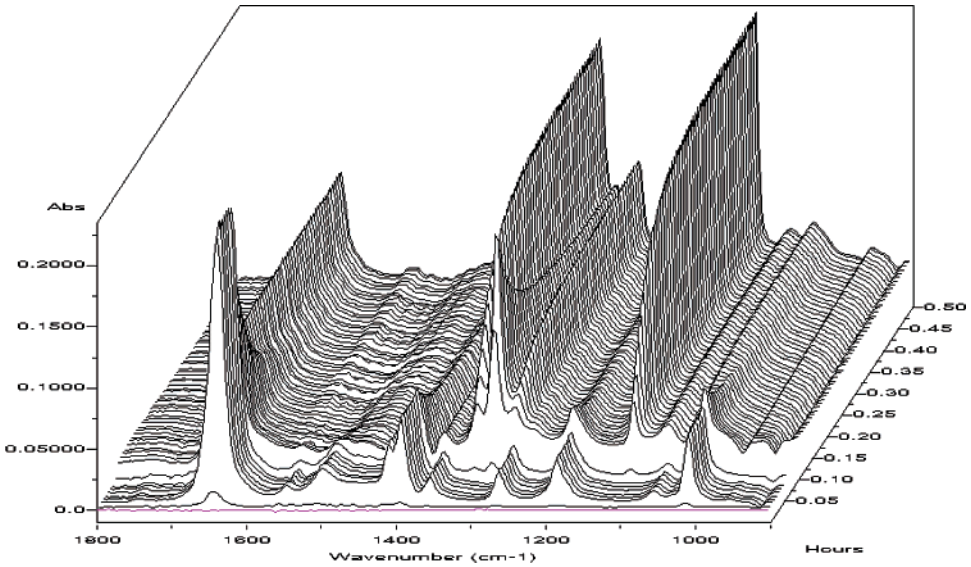


Figure 4. **Stacked FTIR spectra collected during first 30 min of the reaction of $POCl_3$ with DMA.**

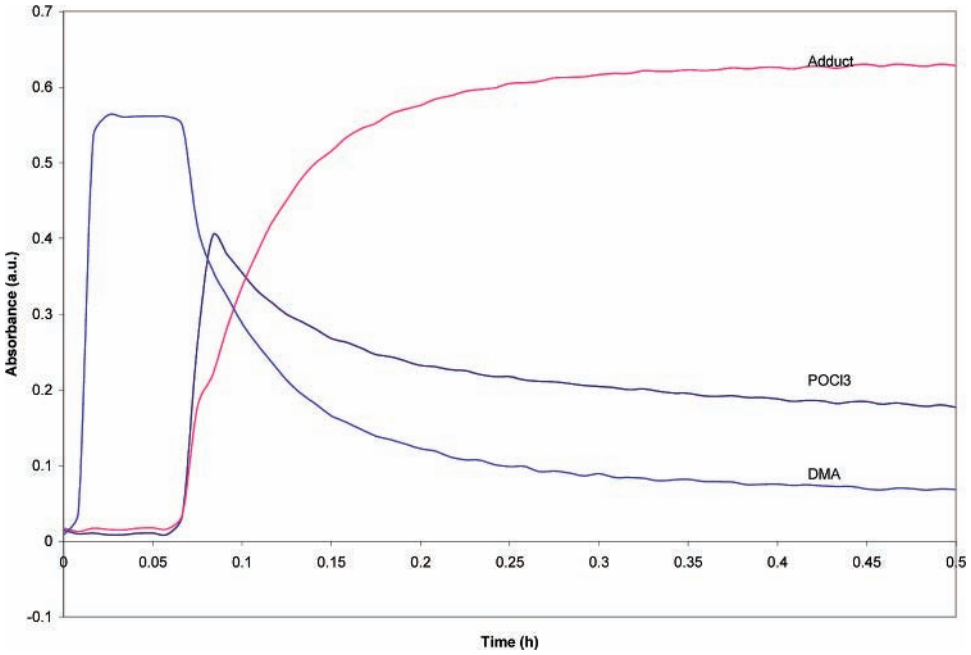


Figure 5. **Reaction profile for addition of $POCl_3$ to DMA in ACN.**

of the organic layer. The API (**1**) was isolated from IPA in a yield of 98% with a purity of >99.5% (AN HPLC).

React-IR Investigation of the Reaction between $POCl_3$ and DMA. Owing to the extended processing times normally encountered on scale, it is imperative that addition times be stressed during the development stage to ensure that the process will stand up to the inevitably longer addition times required on scale. In the present case, the final step in the synthesis of the API required that a reactive iminium species be generated and added to the penultimate intermediate. The stress tests discussed earlier indicated that the process would be robust to long addition times; however, a method to access the stability of the iminium species was preferred.

The reaction between DMA and $POCl_3$ was investigated using in situ FTIR monitoring. Briefly, DMA was added to a reaction cell that was fitted with a ReactIR DiComp probe. A few scans were collected to establish the IR spectrum of DMA, and then $POCl_3$ was added while the temperature was maintained. Figure 4 shows a stacked plot of the 900−1800 cm^{-1} spectral region collected during the first 30 min of the reaction. The initial growths at 1620 and 1400 cm^{-1} were due to addition of DMA to the acetonitrile-containing cell. The addition of $POCl_3$ led to an initial growth at 1300 cm^{-1}, which then decreased in intensity. This spectrum matched that of $POCl_3$, and the fact that it grew and then decayed indicated that the reaction between DMA and $POCl_3$ was not instantaneous. This growth and decay was more obvious in the reaction profile (Figure 5). Examination of the profile also showed that the reaction between DMA and $POCl_3$ required 20−30 min to go to completion, even though the addition of $POCl_3$ was quite rapid. As $POCl_3$ was added, the peaks due to DMA decreased in intensity, and a new species formed as indicated by the peak at 1663 cm^{-1},

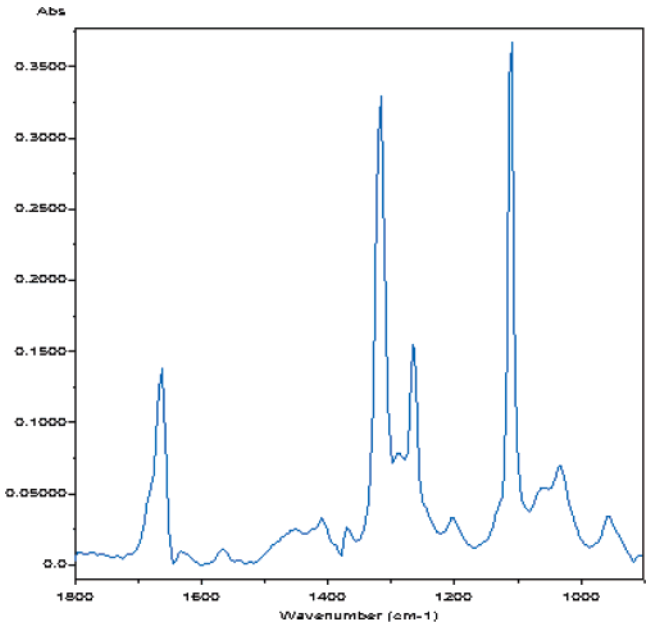


Figure 6. **IR spectrum of species formed during the reaction of DMA and $POCl_3$.**

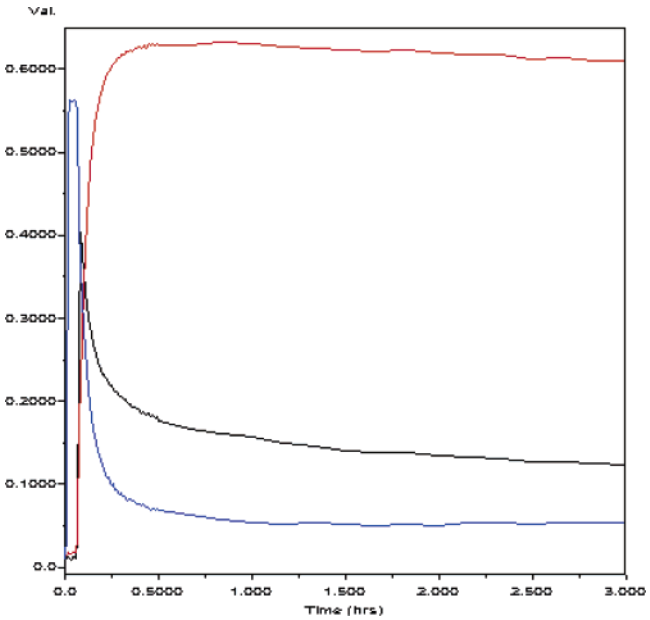


Figure 7. **Extended reaction profile.**

consistent with an iminium salt.[19] The IR spectrum of the new species is shown in Figure 6.

When the analysis of the reaction was extended to 3 h (Figure 7), a trend showing a decrease in the concentration of the iminium species was evident. Since the mixture remained homogeneous, this decrease in concentration was not due to precipitation of the complex and appeared consistent with decomposition of the intermediate. Decomposition of the complex due to adventitious water was ruled out since the concentration of DMA did not increase.

The formation and stability of the iminium complex was evaluated with a reaction calorimeter (RC-1) and an Advanced Reactive System Screening Tool (ARSST). For the RC-1 experiment, 1 equiv of DMA was added over 1 h to a solution of $POCl_3$ in acetonitrile. The exotherm was immediate and directly proportional to the dose of DMA. The total heat output was mild at 42 kJ/mol DMA and represents an adiabatic temperature rise of 86 °C. Addition of DMA to $POCl_3$ did not show any indication of reagent accumulation, and the reaction appeared to be over as soon as the addition of DMA was complete. This is contrary to the results observed with the React-IR which clearly showed accumulation of $POCl_3$. These differing results are likely due to the longer addition period used for the RC-1 experiment rather than due to the different order of addition.

An 8-mL aliquot of the RC-1 contents was placed in an ARSST bomb which was then charged to 207 psi with nitrogen. The temperature was increased to 200 °C over 90 min and then returned to ambient temperature. Figure 9 shows the temperature and pressure profile from the ARSST. Although there were no thermal events, the pressure profile indicates that a gas was generated. Above 120 °C, the pressure increase accelerated rather than increasing linearly with temperature. Additionally, the pressure dropped to 215 psi rather than returning to 207 psi when the contents were returned to ambient temperature.

Conclusion

A concise route to an α adrenoceptor antagonist that displayed selectivity for the 1_A and 1_B subtypes was developed and demonstrated in a pilot plant. Keys to the success of the route were (1) the development of catalytic hydrogenation conditions that allowed a substrate of low solubility to be reduced and separated from the catalyst and (2) activation of dimethylacetamide with $POCl_3$ for installation of the amidine functional group. The reaction between $POCl_3$ and DMA was shown to be quite fast, but not instantaneous, when $POCl_3$ was added quickly to DMA. The reaction required 20−30 min to be complete, and the generated iminium salt was determined to be sufficiently stable to warrant its use on a large scale; however, slow decomposition was observed. Addition of DMA to $POCl_3$ over a 1 h period did not lead to accumulation of DMA. The reaction between DMA and $POCl_3$ was determined to be moderately exothermic with an T_{ad} of 86 °C. Our studies showed that decomposition of the DMA−$POCl_3$ complex did not result in any significant thermal events. Decomposition of the complex manifests itself as incomplete conversion to the amidine, a situation that is easily overcome by using excess complex for the reaction.

Experimental Section

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

2,4-Dichloro-6,7-dimethoxy-5-methyl-quinazoline (6). 6,7-Dimethoxy-5-methyl-1H-quinazoline-2,4-dione (4.54 kg, 19.2 mol, 1.0 equiv), acetonitrile (28 kg), and phosphorus oxychloride (11.7 kg, 4 equiv) were combined and adjusted

(19) Simple iminium salts have a characteristic C=N stretching band at 1640−1700 cm^{-1} (See Merenyi, R. Iminium Salts in Organic Chemistry, Part 1. *Advances in Organic Chemistry*; John Wiley: New York, 1979; Vol. 9, Chapter 2, pp 23−106.

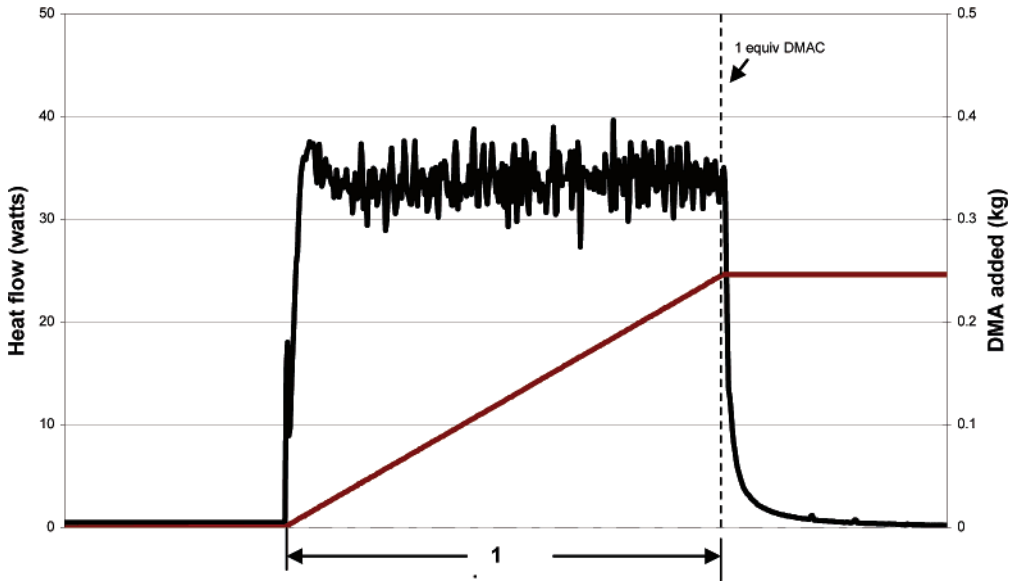


Figure 8. **RC-1 heat flow for addition of DMA to $POCl_3$ in acetonitrile.**

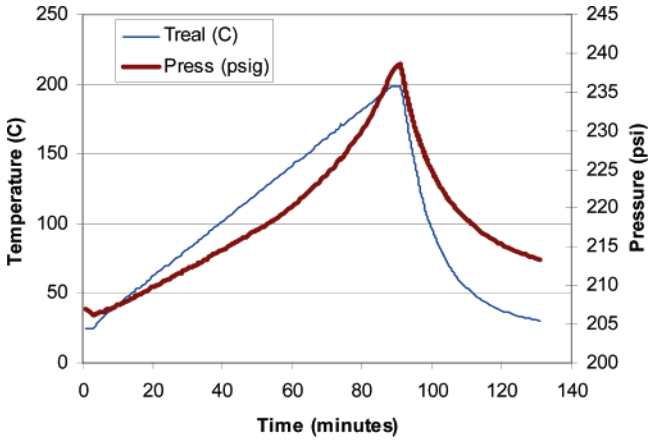


Figure 9. **Temperature and pressure profile for iminium species determined with ARSST.**

to reflux. After 18 h, in-process analysis indicated the reaction was complete. The mixture was cooled to ca. 5 °C and then added to a reactor containing water (50 L) while the temperature was maintained below 20 °C. Product **6**, which precipitated during the quench, was filtered, rinsed with water, and left on the filter overnight under vacuum while dry nitrogen was blown through the cake. The product was discharged and used as a water-wet cake in the next step (11.0 kg with LOD = 58.37%, estimated 4.58 kg of product (87% yield)).

2-Chloro-6,7-dimethoxy-5-methyl-1H-quinazolin-4-one (2). Water-wet **6** (11 kg, containing 4.58 kg of **6**, 16.6 mol) was suspended in a mixture of THF (35 kg) and water (32 L). Potassium hydroxide (7.3 kg, 64.8 mol, 3.9 equiv) was added, and the mixture was stirred at 20−25 °C for 18 h (overnight). The bulk of the THF was distilled under vacuum and replaced with water (ca. 30 kg). Acetic acid was added until the pH was 6−7.[20] The reactor contents were adjusted to ca. 80 °C and then cooled to ca. 20 °C, filtered, washed with water (3 × 30 L), and dried under vacuum at 70 °C to afford 4.15 kg of **2** (98% yield) with 94% purity (4.5% dione **5** present). A recrystallized sample had the following analytical results: Anal. Calcd For $C_{11}H_{11}ClN_2O_3$: C, 51.88; H, 4.35; N, 11.00. Found: C, 51.87; H, 4.30; N, 11.00. mp 253−254 °C.

2-[(3-Nitro-benzyl)-methyl-amino]-6,7-dimethoxy-5-methyl-1H-quinazolin-4-one (7). Chloroquinazolinone **2** (3.59 kg, 14.1 mol, 1.0 equiv), methyl-(3-nitrobenzyl)amine hydrochloride (3.30 kg, 16.3 mol, 1.15 equiv), and diisopropylethylamine (4.71 kg, 36.4 mol, 2.5 equiv) were combined in 2-propanol (35 kg) and heated at reflux for 24 h. Water (15 L) was added, and the reaction mixture was cooled to 22 °C over ca. 6 h and then filtered, rinsed with IPA/water (1:1 v/v), and dried to yield 5.11 kg of **7** (94% yield) having a purity of 98% (AN HPLC). Anal. Calcd For $C_{19}H_{20}N_4O_5$: C, 59.37; H, 5.24; N, 14.58. Found: C, 59.19; H, 5.18; N, 14.29; mp 262−264 °C; MS: *m*/*z* (ESI): 385 ($M^{\bullet+}$ + 1).

2-[(3-Amino-benzyl)-methyl-amino]-6,7-dimethoxy-5-methyl-1H-quinazolin-4-one (8). Compound **7** (5.11 kg, 13.3 mol, 1.0 equiv), palladium on carbon (400 g, 10% palladium, 50% water-wet), THF (47 kg), MeOH (12 kg), and NaOH (1.1 kg, 50% solution, 13.8 mol, 1.0 equiv) were combined and stirred at 22 °C for ca. 30 min. The atmosphere inside the reactor was converted from nitrogen to hydrogen,[21] and the mixture was stirred for 2.5 h, after which time in-process analysis indicated the reaction was compete. The hydrogen atmosphere was exchanged with nitrogen, the catalyst was removed by filtration, and the reactor was rinsed with methanol (14 kg). The combined filtrates were concentrated at atmospheric pressure until the distillation temperature was 63−65 °C. The final volume was adjusted to 20−25 L by adding or distilling methanol, and then water (22 L) was added. The temperature was adjusted to 50−55 °C, and acetic acid (1.2 kg, 1.5 equiv) was added. The mixture was adjusted to ca. 22 °C and then filtered, rinsed

(20) At this scale, 4.1 kg of acetic acid was required.

(21) **Caution!** This reaction is exothermic. At this scale, a 7 °C temperature rise was observed over 40 min.

with methanol/water (1:1 v/v), and dried in vacuo at 75 °C to afford **8** (4.54 kg, 96% yield). Purity = 99.4 AN HPLC. Anal. Calcd For $C_{19}H_{22}N_4O_3$: C, 64.39; H, 6.26; N, 15.81. Found: C, 63.96; H, 6.26; N, 15.59; mp 271−274 °C; MS: *m*/*z* (ESI): 355 ($M^{\bullet+}$ + 1).

***N′*-(3-{[(6,7-Dimethoxy-5-methyl-4-oxo-1,4-dihydroquinazolin-2-yl)-methyl-amino]-methyl}-phenyl)-*N*,*N*-dimethyl-acetamidine (1).** *N*,*N*-Dimethylacetamide (2.47 kg, 28.3 mol, 2.5 equiv) was added to a cooled (ca. 10 °C) solution of phosphorus oxychloride (4.36 kg, 28.3 mol, 2.5 equiv) and acetonitrile (3.14 kg) with the temperature maintained below 20 °C.[22] The resulting mixture was stirred at 10−20 °C for ca. 1 h and then added to a cooled (ca. 10 °C) mixture of **8** (4.01 kg, 11.31 mol, 1.0 equiv) in dichloromethane (53 kg) as the temperature was maintained below 20 °C. The mixture was stirred at ca. 20 °C for ca. 1 h, after which time in-process analysis indicated the reaction was complete. The reaction mixture was cooled to ca. 10 °C, then water (60 L) was added, and the pH was adjusted to 8−9 by the addition of sodium hydroxide (11.35 kg, 50% aqueous solution).[23] The layers were then separated, and the aqueous layer was extracted with dichloromethane (16 kg). The combined organic layers were combined, washed twice with water (40 L), separated, and transferred to a clean vessel. 2-Propanol (32 kg) was added, and the resulting solution was concentrated at atmospheric pressure with a maximum jacket temperature of 90 °C until the internal volume was ca. 40 L. The reactor contents were adjusted to 80 °C and maintained at that temperature for 2−3 h and then cooled to 15 °C over 10 h. The reactor contents were aged at 15 °C for 4 h and then filtered, rinsed with 2-propanol (18 kg), and dried under vacuum at 75 °C until the LOD was <0.5%. Total product was 4.43 kg (92.5% yield), purity 99.9% (AN HPLC). Anal. Calcd For $C_{23}H_{29}N_5O_3$: C, 65.23; H, 6.90; N, 16.54. Found: C, 65.27; H, 6.80; N, 16.54; mp 188 °C (Form B); MS: *m*/*z* (ESI): 424 ($M^{\bullet+}$ + 1).

(22) At this scale, the addition required 30 min with 5 °C aqueous glycol circulating through the reactor jacket.

(23) It is important that the pH remain above 8 for at least 30 min after the pH adjustment. The pH had a tendency to drift lower following initial adjustments into the specified pH range.

Acknowledgment

We are grateful to Dr. Yvonne Walbroehl, Tim Lane, Tina Nguyen, and Larry Hennessy for providing analytical support for this project. The Palo Alto Pilot Plant staff of Gary Hedden, Gary Byrge, Jesus Dela Paz, Francis Onyegegbu, Gaudelio Salom, and Viel Teixeira is also thanked for their contributions during the pilot plant campaigns.

Received for review July 15, 2005.

OP050122H