Organic Process Research & Development

ARTICLE

pubs.acs.org/OPRD

First, Second, and Third Generation Scalable Syntheses of Two Potent H_3 Antagonists

Daniel J. Pippel,* John E. Mills, Chennagiri R. Pandit, Lana K. Young, Hua M. Zhong, Frank J. Villani, and Neelakandha S. Mani

Johnson & Johnson Pharmaceutical Research and Development, L.L.C., 3210 Merryfield Row, San Diego, California 92121, United States

Supporting Information

ABSTRACT: Our teams have recently completed scale-up campaigns for two structurally similar H_3 receptor antagonists. The first and second generation processes were developed for the synthesis of 107 and 125 g batches of (4-cyclobutyl-1,4-diazepan-1-yl)(6-(4-fluorophenoxy)pyridin-3-yl)methanone·HCl (**1·HCl**). A third generation process was utilized for production of 104 g of 3-((5-(4-cyclobutyl-1,4-diazepane-1-carbonyl)pyridin-2-yl)oxy)benzonitrile·HCl (**2·HCl**). The evolution from first to second generation process was driven by a desire to minimize cost of goods through employment of symmetrical homopiperazine rather than a more expensive monoprotected variant. Project demands for a late stage intermediate that could provide **1** or **2** led to additional route scouting and the ultimate determination of a third scalable synthesis for these types of molecules. The use of a lithium alkoxide for Lewis base catalysis of an ester to amide transformation represents a key improvement for the third generation synthesis.

INTRODUCTION

The H_3 receptor has emerged as a promising target within the neuroscience community; antagonism of this G-protein-coupled receptor could have therapeutic applications for various disease-states including narcolepsy, ADHD, Alzheimer's disease, and obesity.[1−3] With the phenomenal success of other histamine receptor antagonists including Claritin and Benadryl (H_1 receptor antagonists), as well as Tagamet and Zantac (H_2 receptor antagonists), excitement over a potential third class of antihistamine drugs has resulted in a large body of work spanning the laboratories of academic groups, biotechnology companies, and several pharmaceutical companies.[4] Internally, our medicinal chemistry team has developed several series of H_3 receptor antagonists, including recently disclosed hydroxyproline-based and aryloxypyridine-based ligands.[5−7] Of the aryloxypyridine-based H_3 receptor antagonists, two compounds, **1** and **2**, were chosen for in-depth profiling based on binding affinity, brain penetration, and microsomal stability (Figure 1). Scale-up development of these two compounds forms the focus of this paper.

Compound **1** was initially synthesized in just 2 steps (not including the preparation of *N*-cyclobutylhomopiperazine **5**) by our medicinal chemistry counterparts. Nucleophilic aromatic substitution of 5-bromo-2-fluoropyridine (**3**) with 4-fluorophenol was followed by Larhed aminocarbonylation of **4** under microwave conditions with **5** and carbon monoxide generated in situ from molybdenum hexacarbonyl (Figure 2).[7−10] This route provided the starting point for our investigations.

RESULTS AND DISCUSSION

Although the sequence shown in Figure 2 was quite elegant and concise, in considering a potential manufacturing route,

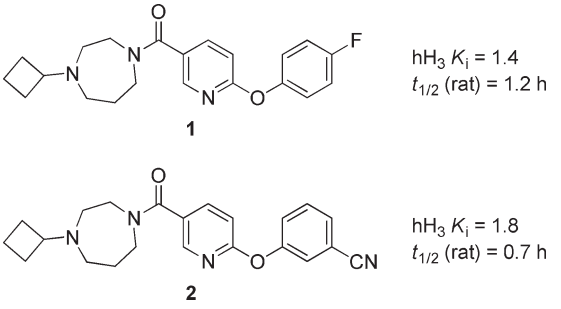


Figure 1. Structures of H_3 receptor antagonists **1** and **2**.

several factors drove us to pursue an alternative. First, even though 5-bromo-2-fluoropyridine (**3**) is readily available and inexpensive, we did not believe it could ultimately compete with 6-chloronicotinic acid (or its simple derivatives) from a cost perspective.[11] Several key intermediates utilized in the synthesis of common herbicides and the neonicotinoic class of insecticides are closely related to 6-chloronicotinic acid,[12] and it is available in two simple steps from 3-picoline (chlorination to the corresponding chloro(trichloromethyl)pyridine and hydrolysis).[13] Second, the opportunity to replace a palladium-mediated aminocarbonylation in the final step with a simple amide bond forming reaction seemed desirable in light of the potential for metal residues. Third, the chromatography employed after the medicinal chemistry aminocarbonylation would not be suitable for large-scale synthesis.

Received: January 6, 2011
Published: March 12, 2011

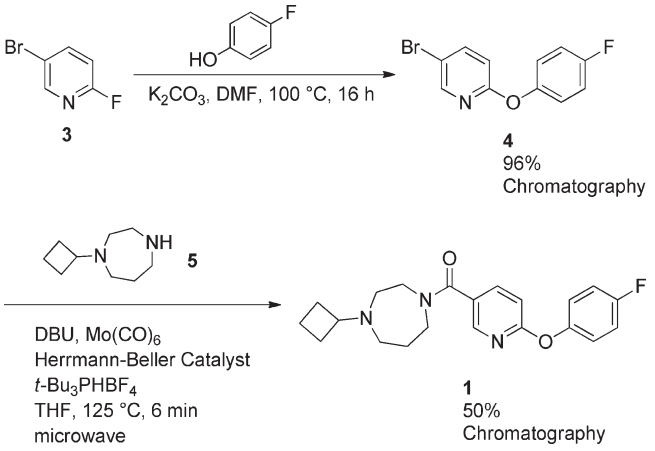


Figure 2. Synthesis of **1** through S_NAr and aminocarbonylation reactions.

With this alternative route in mind, a first generation synthesis to **1·HCl·H$_2$O** (Figure 3) was developed. Preparation of the *N*-cyclobutylhomopiperazine dihydrochloride salt (**5·2HCl**) was straightforward, proceeding in 86% yield over two steps. Reductive amination of cyclobutanone with commercially available *N*-Boc-homopiperazine (**6**) and sodium triacetoxyborohydride afforded **7** as a semisolid. Treatment of **7** with 4 N HCl in dioxane afforded **5·2HCl** as a hygroscopic off-white solid. This diamine and the commercially available 6-chloronicotinyl chloride (**8**) were then subjected to Schotten−Baumann conditions to form the amide **9** as an oil in 91% yield. Isopropyl acetate was chosen as the organic solvent for this reaction based on comparison with toluene and THF. In the case of the former, the nicotinyl chloride **8** was not completely soluble; in the case of the latter, hydrolysis of **8** was observed. Nucleophilic aromatic substitution of **9** with 4-fluorophenol at 100 °C in DMA with 2 equiv of cesium carbonate provided the desired H_3 receptor antagonist **1** in 76% yield as an oil. Reactions with potassium carbonate or less than 2 equiv of cesium carbonate did not reach completion. The need for a crystalline salt form of the final product was addressed with a screening campaign that ultimately led to a mono HCl, monohydrate of **1**. Salt formation was conducted with **1** in ethanol and 2 M HCl in ether as the acid source to provide **1·HCl·H$_2$O** in 82% yield. The largest campaign with this route provided 107 g of the final product.[14]

This first generation scale-up synthesis was more than adequate for progression of the project through initial stage preclinical tolerance studies. However, when planning for the synthesis of the first GMP kilogram-scale batches, our team reassessed the process. From a cost-of-goods perspective, it was clear that Boc-homopiperazine (**6**) was not an optimal starting material as it is up to 25 times more expensive than the parent homopiperazine.[15] Additionally, employment of homopiperazine directly would obviate a Boc removal step. Finally, a GMP version of the first generation synthesis would most likely have led to outsourcing cyclobutylhomopiperazine·2HCl (**5·2HCl**), which is hygroscopic and difficult to handle, making it a poor choice as a regulatory starting material.

With the desire to utilize the least expensive possible diamine starting material as a primary driver, our team developed the synthesis shown in Figure 4. An initial S_NAr reaction between ethyl-6-chloronicotinate (**10**) and 4-fluorophenol provided the

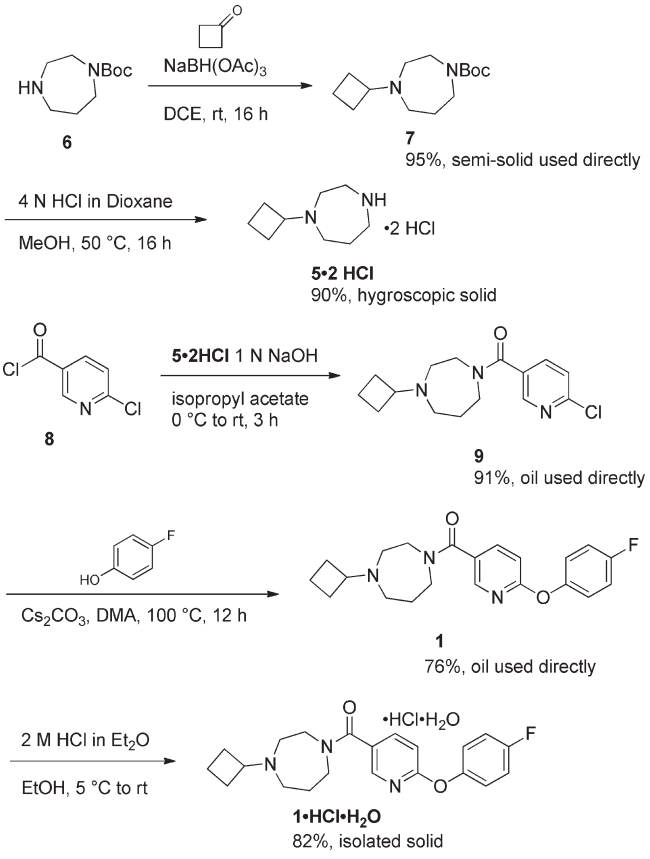


Figure 3. First generation scale-up synthesis of **1·HCl·H$_2$O**.

heteroaryl−aryl ether linkage in ethyl 6-(4-fluorophenoxy) nicotinate (**11**). Subsequently, in the key step of the sequence, homopiperazine was allowed to react directly with the ethyl ester **11** to provide the desired diazapanylamide **12**. In this reaction, a solution of the ethyl ester **11** and 2.4 equiv of homopiperazine were cooled to 0 °C and hexyllithium (1.5 equiv, 2.3 M in hexane) was slowly added. The order of operations is critical in this reaction as addition of the hexyllithium to the homopiperazine followed by addition of the ester to the lithium amide results in formation of a small amount of a des-fluoro amide byproduct. Not surprisingly, even under optimized conditions, the reaction does produce some of the expected diamide byproduct.[16] However, this diamide can be removed by repeated extractions of a pH 2 aqueous layer with MTBE. Thus, with the appropriate extraction and crystallization protocol, **12** is provided as a free-flowing solid in 56% yield. Final-stage reductive amination of cyclobutanone with **12** and salt formation gave rise to **1·HCl·H$_2$O** in 69% yield, on 125 g scale.[14]

Because the desymmetrization of homopiperazine is not a trivial problem, we were especially pleased with this second generation synthesis.[6b,17] Also, direct ester to amide transformation is arguably underutilized.[18−20] Another advantage of this route is the introduction of the most expensive piece on a molar basis, cyclobutanone, in the final chemical transformation.

As the 4-fluorophenoxy analog **1** continued to progress through biological profiling, it became apparent that our H_3 receptor antagonist team was also interested in the closely related 3-cyanophenoxy analog **2**.[7] In fact, the team became motivated to design a synthesis that could proceed to either **1**, **2**, or a similar

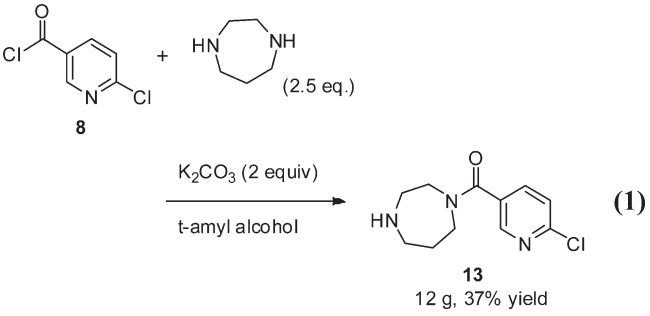
dx.doi.org/10.1021/op200005e |*Org. Process Res. Dev.* 2011, 15, 638–648

analog via a common late-stage intermediate. Such a route would provide maximum flexibility as the project continued to move forward. Unfortunately, the second generation synthesis of **1** did not meet this requirement as the differentiation of the aryl ether group occurred in the first step.[21] Clearly, an alternate approach, which featured a final step heteroaryl−aryl ether bond formation, was required. The retrosynthetic analysis shown in Scheme 1 was proposed as an alternative to the first generation route.

Here, the key step is base-mediated reaction between 6-chloronicotinyl chloride (**8**) or ethyl 6-chloronicotinate (**10**) and homopiperazine to generate **13**. However, in addition to the desired **13**, one can imagine many potential side products (Scheme 2). These unwanted side products were anticipated based on two modes of possible reactivity. First, homopiperazine has the capacity to react at both termini to form pseudodimer **14**. Second, since the 6-chloro group on the nicotinic acid derivative is potentially labile, byproduct **15** is easily conceived. In the ethyl 6-chloronicotinate case, side products **16**, **17**, and **18** are also possible. Further, combinations of the two modes of byproduct generation, as well as potential incorporation of the base were also feared.

The reaction between **8** and homopiperazine was explored under a variety of conditions as shown in Table 1. With triethylamine as a base, the product distribution ranged from exclusively pseudodimer **14** in THF to a ∼1:1 ratio of product **13** to pseudodimer **14** in *tert*-amyl alcohol (Table 1, entries 1−5). Several inorganic bases were also screened with *tert*-amyl alcohol (Table 1, entries 6−8). The case with 2 equiv of potassium carbonate (Table 1, entry 8) provided the optimal product **13** to pseudodimer **14** ratio of 1.7:1. Interestingly a reaction with no base at all (Table 1, entry 9) afforded identical results. All reactions displayed clean HPLC profiles and proceeded to completion.

With these results in hand, the *tert*-amyl alcohol/K_2CO_3 conditions shown in Table 1, entry 8, were scaled to 12 g, and the desired product **13** was obtained in 37% yield (eq 1). Removal of pseudodimer **14** was possible without chromatography as the product could be selectively extracted into a pH 3.74 buffer (NaOAc/HOAc).



(1)

Despite this success, we still hoped to improve the yield through minimization of pseudodimer **14** formation. Our initial

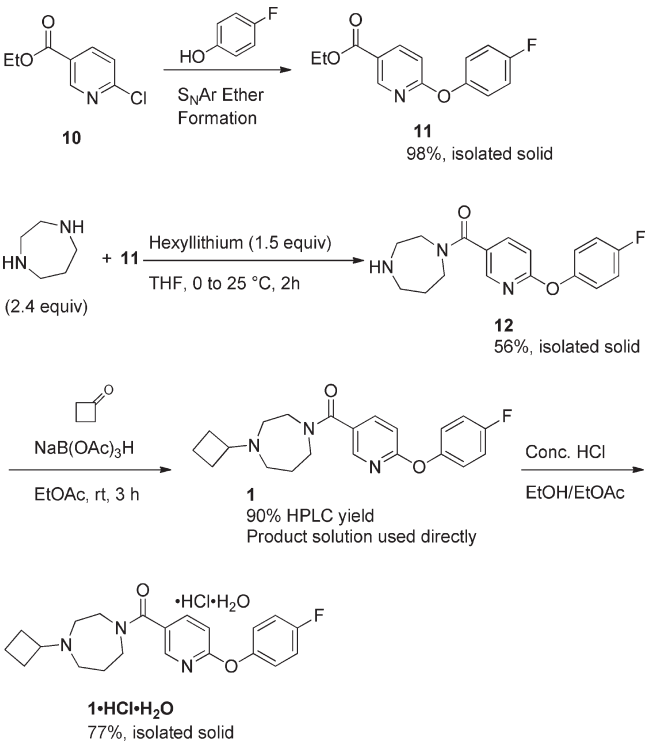
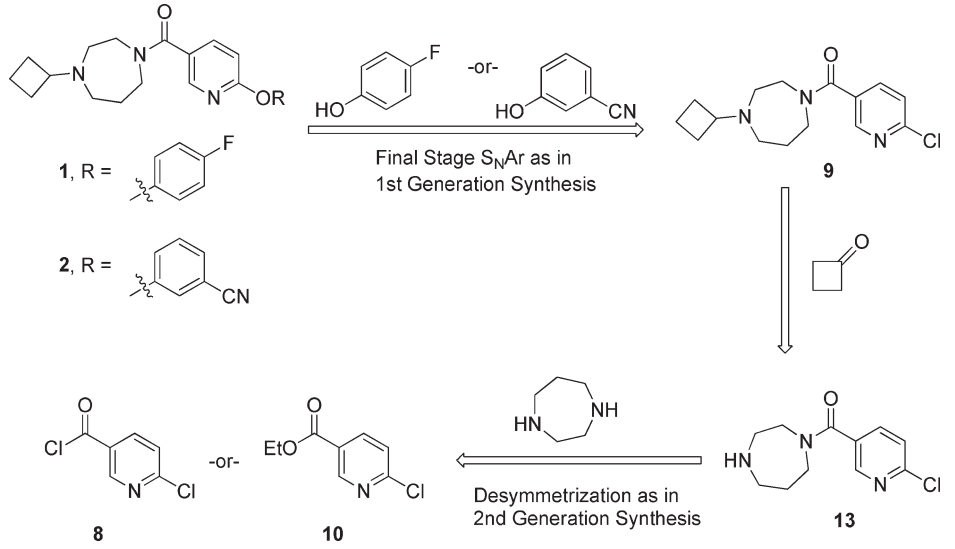


Figure 4. Second generation scale-up synthesis of $1 \cdot HCl \cdot H_2O$.

Scheme 1. Retrosynthetic Analysis for Third Generation Synthesis of 1 and 2



dx.doi.org/10.1021/op200005e |*Org. Process Res. Dev.* 2011, 15, 638–648

Scheme 2. Potential Products in Reaction between 6-Chloronicotinic Acid Derivatives and Homopiperazine

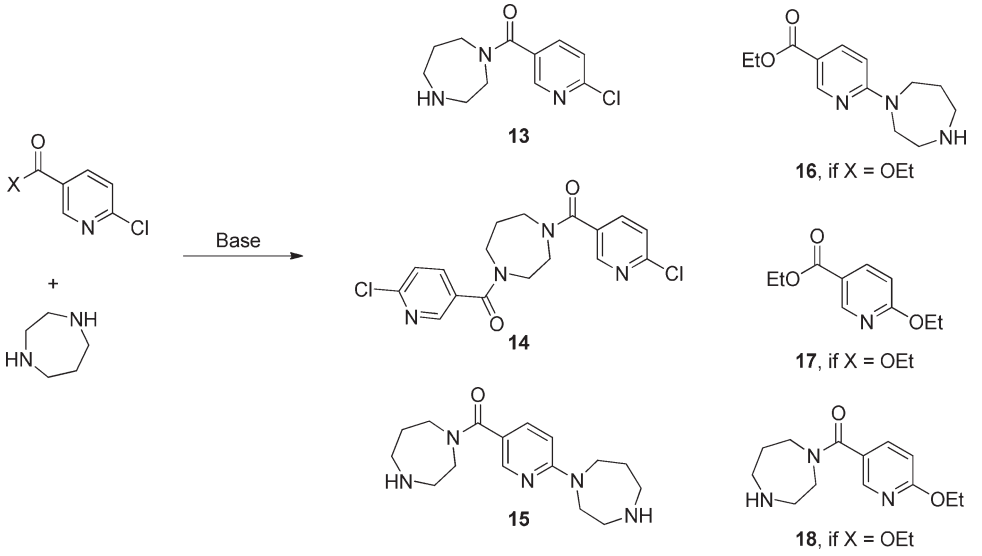
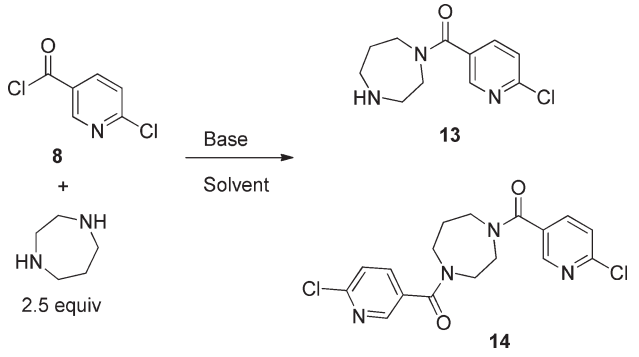


Table 1. Formation of Amide 13 from 8 and Homopiperazine



entry[a]	base (equiv)	solvent	product ratio (**13**:**14**)[b]
1	triethylamine (1)	THF	**14** only
2	triethylamine (3)	THF	1:11.2
3	triethylamine (1)	DCM	1:2.3
4	triethylamine (1)	ACN	1:1.8
5	triethylamine (1)	*tert*-amyl alcohol	1:1.1
6	2 M $NaOH_{(aq)}$ (2)	*tert*-amyl alcohol	1:1.37
7	2 M $Na_2CO_{3(aq)}$ (2)	*tert*-amyl alcohol	1:1.35
8	K_2CO_3 (2)	*tert*-amyl alcohol	1.7:1
9	none	*tert*-amyl alcohol	1.7:1

[a] In entries 1−6 and 9 homopiperazine, (base), and solvent were stirred under N_2 (g) at 0 °C and then a solution of 6-chloronicotinyl chloride was slowly added. In entries 7 and 8, solid 6-chloronicotinyl chloride was slowly added at room temperature. [b] Ratios are based on calibrated HPLC area response.

experiments had been conducted with nicotinyl chloride **8** because we reasoned that the acid chloride functional group would be more reactive than the ethyl ester group in **10**, which could help to minimize reactions at the 6-chloro position. However, because that enhanced reactivity seemed to promote pseudodimer formation, we chose to explore reactions between **10** and homopiperazine.

Thus, **10** and homopiperazine were premixed and then treated with hexyllithium, exactly according to the previous instance with **11** and homopiperazine (Table 2, entry 1). In fact, **13** was generated as the primary product in a 8:1 ratio with pseudodimer **14**; however, this reaction was not nearly as clean as the case with *tert*-amyl alcohol/potassium carbonate. Preformation of the lithium amide followed by addition of the ester **10** minimized pseudodimer **14** formation further (14:1, **13**:**14**), and the crude product was purified by flash chromatography to provide a 60% yield of material that was 88 wt % **13** and 12 wt % **16** (Table 2, entry 2).[22,23]

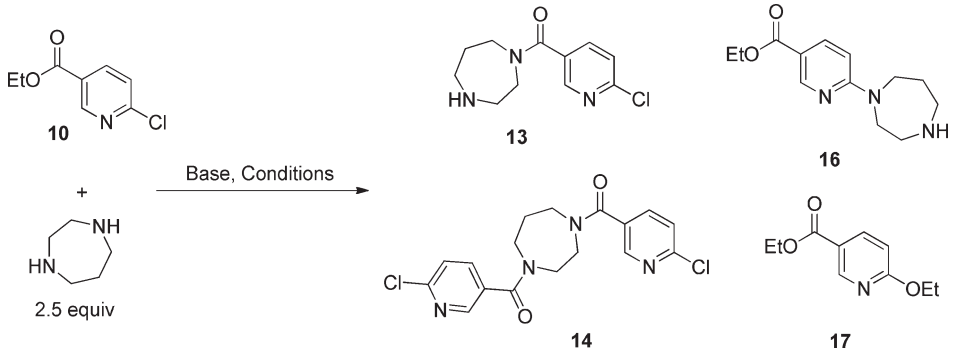
With *i*-PrMgCl as an alternative base, the reaction was quite clean providing exclusively product **13** and pseudodimer **14**; however, the **13**:**14** ratio was just 2.5:1 (Table 2, entry 3). Recalling the reasonably successful reaction between 6-chloronicotinyl chloride (**8**) and homopiperazine in the absence of base (Table 1, entry 9), a base-free reaction with ethyl 6-chloronicotinate (**10**) was also attempted. In this case, **16** is the exclusive product, isolated in 83% yield, with no formation of **13** (Table 2, entry 4).

A scale-up of the conditions shown in Table 2, entry 2 (preformation of the lithium amide and then addition of the ester **10**) to a 20 g scale resulted in an unexpectedly low yield (46%) and significant formation of side product **17**, which previously had not been seen to any significant extent (Table 2, entry 5). In an attempt to understand the unexpected behavior, varying equivalents of *n*-hexyllithium were screened on small-scale.[24] HPLC yields for the reactions indicated that 0.5 equiv of base is sufficient to push the reaction to completion, and excess base contributes to complex reaction profiles (Table 2, entries 6 and 7).[25]

Although we were delighted to have improved the yield of the small-scale reaction in an unexpected way (substoichiometric base), we were still stymied in our attempts to scale up the reaction. In fact, a 20 g reaction with 0.5 equiv of base gave results only moderately superior to those shown in entry 5, again with

dx.doi.org/10.1021/op200005e |*Org. Process Res. Dev.* 2011, 15, 638–648

Table 2. Formation of Amide 13 from 10 and Homopiperazine



entry	base (equiv)	conditions[a]	yield of **13**, %	comments[b,c]
1	*n*-hexyllithium (1.05)	A, 1 g scale	58[d]	**13**:**14** = 8:1
2	*n*-hexyllithium (1.05)	B, 1 g scale	60[e]	**13**:**14** = 14:1
3	*i*-PrMgCl (1.05)	C, 1 g scale	59[e]	**13**:**14** = 2.5:1
4	none	D, 1 g scale	0	83%[e] of **16**
5	*n*-hexyllithium (1.05)	B, 20 g scale	46[e]	**17** is major side pdt
6	*n*-hexyllithium (0.5)	B, 1 g scale	75[d]	clean reaction
7	*n*-hexyllithium (2.0)	B, 1 g scale	45[d]	messy reaction
8	*n*-hexyllithium (0.5)	B, 20 g scale	57[e]	**17** is major side pdt
9	*n*-hexyllithium (0.5)	A, 20 g scale	73[e]	no **17** observed

[a] In condition A, homopiperazine and **10** were premixed and then base was added at 0 °C. The reaction was then warmed to room temperature and held for 2−16 h. In condition B, homopiperazine and base were premixed and then the electrophile **10** was added at 0 °C. The reaction was then warmed to room temperature and held for 2−16 h. In condition C, the conditions were identical to B, but with no warming after addition of the ester and quenching after 1 h. In condition D, the reaction was warmed to 40 °C overnight. [b] In every case (except entries 3 and 4) impurity **16** is formed at about 5−10%. [c] Ratios of **13** to **14** are based on calibrated HPLC area response. [d] Yield by quantitative HPLC with internal standard. [e] Isolated yield.

significant formation of **17** (Table 2, entry 8).[26] In an attempt to duplicate the large-scale reaction failure on small scale, the reaction was stressed in the following ways: addition of 2 mol % of $Pd(OAc)_2$ (to test the effect of possible trace Pd contamination of our glassware), addition of 10 mol % of water, poor stirring, and aging of the lithium amide for several hours prior to the addition of the ester **10**. The only case that duplicated the large-scale failure with formation of **17** was the reaction that incorporated aging of the reaction mixture prior to ethyl ester **10** addition. It seems likely that the cause of the failures upon scale-up or on small scale with extended aging relates to aggregation states and possible precipitation of the homopiperazine lithium amide. These reactions are not homogeneous.[27]

This result prompted us to return to our original conditions wherein homopiperazine and the ester **10** were premixed prior to addition of the *n*-hexyllithium (Table 2, entry 1). This addition order does result in a slight increase in the level of pseudodimer **14**; however, this problem is more than offset by the fact that impurity **17** is formed only at trace levels upon scale-up to 20 g. An isolated yield of 73% was obtained (Table 2, entry 9).

With this scalable approach to **13**, a third generation synthesis for **1** or **2** was realized (Figure 5). The homopiperazine reaction with ethyl 6-chloronicotinate (**10**) was executed on 250 g scale, and the desired product **13** was isolated in a yield of 69% (after subtracting the mass of a small amount of **16** that remained after the aqueous workup).[28] The reductive amination of cyclobutanone with **13** was conducted in DCE with sodium triacetoxyborohydride and proceeded uneventfully to **9**.[29] Because **9** was not crystalline as its free base, the minor impurities that existed in the **13** product were still present, either unchanged in the case of **14**, or as a reductive amination product in the case of **16**. Thus, a crystalline salt form of **9** was sought for the control strategy. After a brief screen of typically employed acids, purification was, in fact, possible through formation of a solid L-tartrate salt in ethanol. The salt formation proceeded in 87% yield. Recovery of the free base through extraction (1 N NaOH/*i*-PrOAc) proceeded in 89% yield. The overall yield, then, for reductive amination/purification was 77%.

With the key common intermediate in hand, it was possible to generate both **1** (vide supra) and **2** in high yield. In the case of the latter, treatment of the chloroamido pyridine **9** with cesium carbonate and *m*-cyanophenol in dimethylacetamide gave rise to the desired product **2** in 90% yield after ∼24 h at 125 °C. Salt formation was accomplished with anhydrous HCl in IPA to provide **2**·**HCl** as a crystalline solid in 83% yield.[30] It is important to drive the diaryl ether forming reaction to completion, as it is difficult to completely remove the residual chloroamido pyridine **9** starting material through final salt formation.

After completion of the campaign to provide 100 g of **2**·**HCl**, we briefly returned to the homopiperazine reaction with ethyl 6-chloronicotinate (**10**). On the basis of the success with 0.5 equiv of *n*-hexyllithium, the reaction was also explored with use of 1.0 equiv of lithium ethoxide as the base. Gratifyingly, the reaction provided product in the highest quantitative HPLC yield yet obtained, 84%. On 10 g scale, the product was obtained in a calculated yield of 90% after subtracting contributions of

dx.doi.org/10.1021/op200005e |*Org. Process Res. Dev.* 2011, 15, 638–648

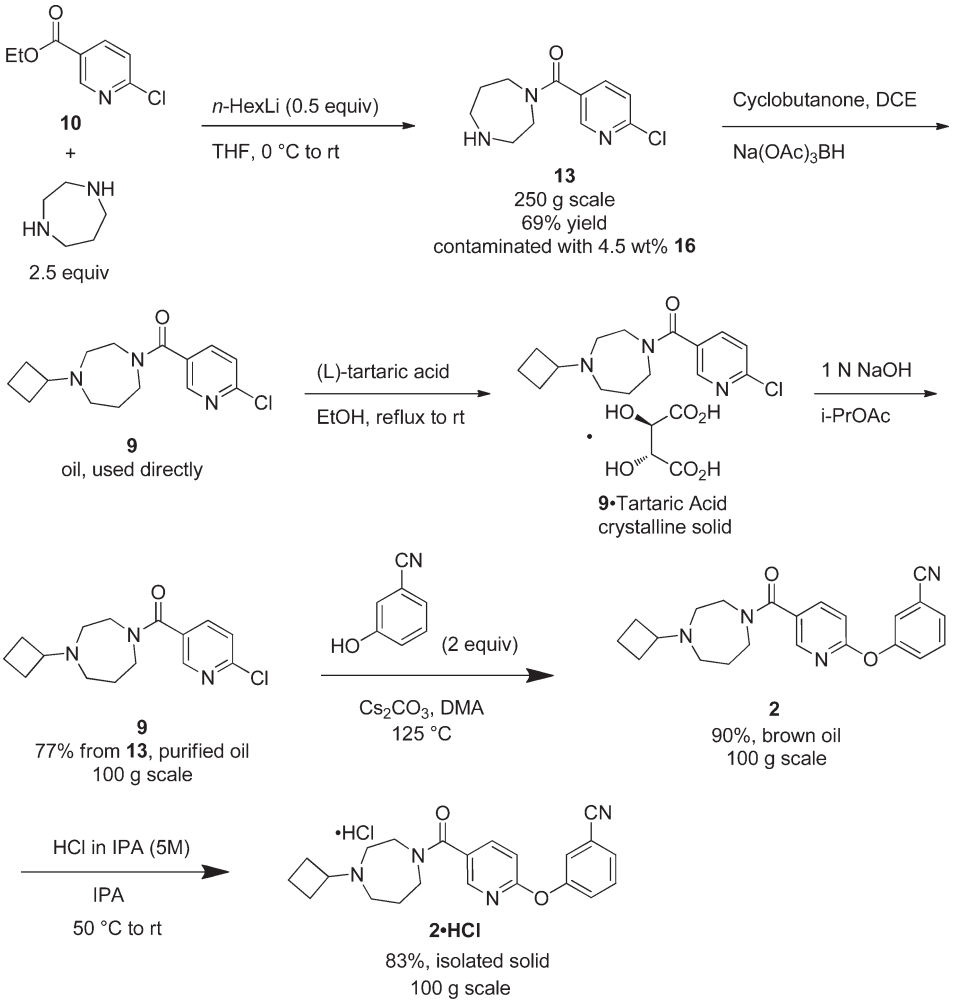
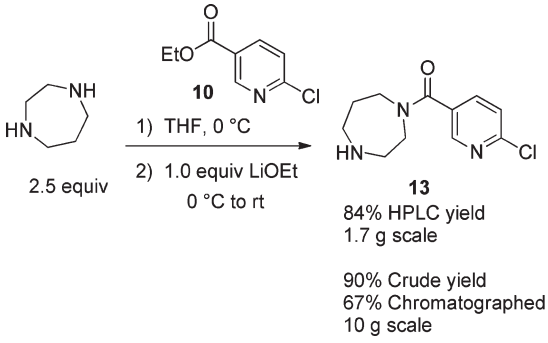


Figure 5. Third generation scale-up synthesis of **2**·**HCl**.

impurities (mostly **16**). An isolated yield of 67% was obtained after reverse phase HPLC (eq 2).[31]



(2)

It is well-known that ester aminolysis may occur through direct reaction between amines and esters under a variety of conditions.[18] Since the reaction is thermodynamically favorable,[32] simple heating of the two components is often enough to affect the reaction. The application of sodium methoxide as a promoter of these reactions was demonstrated in 1937 by Hammett during the course of his work on linear free-energy relationships.[33,34] In light of some of the more exotic variants of this reaction that have been developed lately, this simple Group 1A alkoxide-catalyzed variant may be underutilized.[18,19] The obvious utility of these reactions is in sequences that preferentially proceed through an ester and would otherwise require hydrolysis to the corresponding acid prior to amide bond formation under the control of a coupling system.

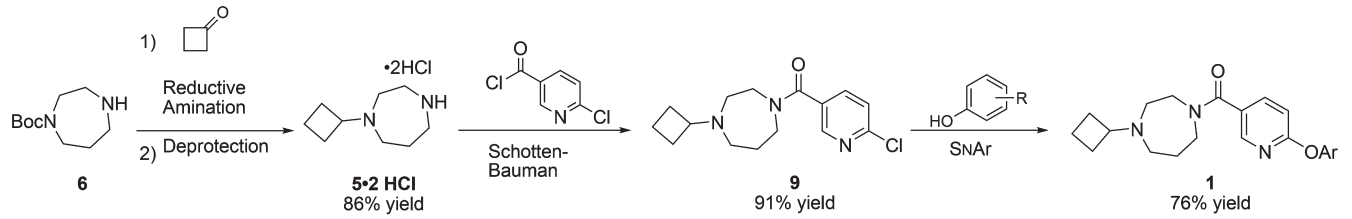
■ SUMMARY

We have demonstrated three independent syntheses for the H_3 antagonist **1** and two syntheses for its analog **2** (Scheme 3). All of the approaches have been demonstrated to at least 100 g scale. We have also identified HCl salt forms for both **1** and **2** that are crystalline and likely suitable for further development. Our first generation approach builds cyclobutylhomopiperazine from *N*-Boc homopiperazine in two steps. Subsequent amidation of a nicotinyl chloride and S_NAr heteroaryl−aryl ether formation complete the synthesis. The route proceeds in four steps with an overall yield of 59% and represents the first chromatography-free synthesis of this class of molecules. Our second generation approach proceeds from four readily available and reasonably priced building blocks to provide **1** in three steps. The three steps were achieved in 48% overall yield. The steps included S_NAr reaction, direct transformation of a nicotinic ester to a nicotinic amide, and reductive amination. The key advance from the first generation synthesis was the employment of homopiperazine directly in the synthesis rather than the much more expensive

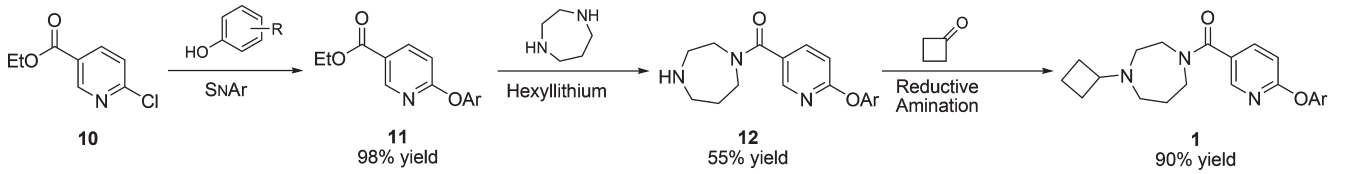
dx.doi.org/10.1021/op200005e |*Org. Process Res. Dev.* 2011, 15, 638–648

Scheme 3. Three Routes to the H_3 Receptor Antagonists 1 and 2

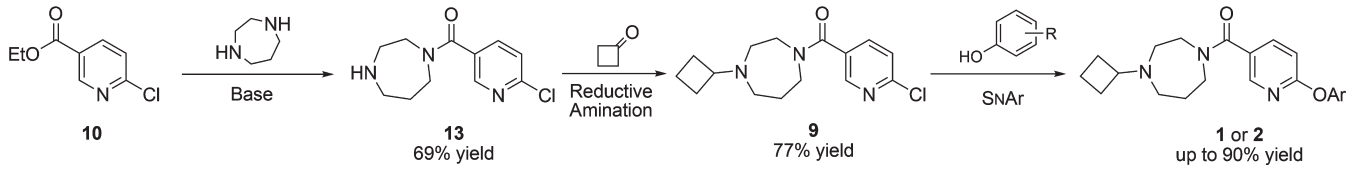
First Generation Synthesis of 1



Second Generation Synthesis of 1



Third Generation Synthesis of 1 or 2



Boc-homopiperazine. Our third generation approach proceeds from the same four building blocks in just three steps to provide **2** in 48% overall yield. These steps include conversion of ethyl 6-chloronicotinate to the corresponding homopiperazine amide, reductive amination of cyclobutanone, and S_NAr reaction to form the appropriate ether linkage. The linchpin step is formation of a novel intermediate, (6-chloropyridin-3-yl)[1,4]diazepan-1-yl-methanone, and is accomplished through an unusual reaction in which ethyl 6-chloronicotinate and homopiperazine (2.5 equiv) are exposed to 0.5 equiv of *n*-hexyllithium, or alternatively, to 1 equiv of LiOEt. The key advantages of the sequence are as follows: (1) concise route with reasonable yields in each step; (2) opportunity for purification of the step 2 product **9** through tartrate salt formation and opportunity for purification of the final step 3 products **1** or **2** through HCl salt formation (overall chromatography-free approach); and (3) progression through a final stage intermediate that is common to both **1** and **2**. Further development activities related to these compounds have provided additional opportunities for our downstream colleagues. Although the second generation route was suitable for direct adaptation to kilogram-scale synthesis, the third generation route was not. In that case, the elimination of undesirable solvents (dichloroethane and dichloromethane), the avoidance of stripping to dryness operations, and a further improved synthesis/isolation of **9** were critical for plant-scale operations. Those achievements will form the focus of a future paper.

EXPERIMENTAL SECTION

HPLC conditions: column—Agilent Eclipse XDB-C8, 5 μm, 4.6 × 150 mm; flow rate—3 mL/min; mobile phases—acetonitrile with 0.05% TFA and water with 0.05% TFA; gradient—5% acetonitrile/95% water to 99% acetonitrile/1% water ramp over 3.8 min, then hold at 99% acetonitrile/1% water for 0.4 min. Hydrochloric acid in 2-propanol was purchased as a 5−6 M solution and used as 5 M. All solvents utilized were purchased in anhydrous form.

First Generation Synthesis: *4-Cyclobutyl[1,4]diazepane-1-carboxylic Acid tert-Butyl Ester (**7**).*[6b] To a solution of Boc-homopiperazine (**6**) (73.0 g, 365.0 mmol) and anhydrous dichloroethane (800 mL) was added cyclobutanone (25.5 g, 363.8 mmol). The pale yellow reaction was stirred at ambient temperature for 1 h, following which, sodium triacetoxyborohydride (92.5 g, 436.3 mmol) was added portion-wise over 1 h. The reaction mixture was stirred for 48 h. $NaOH_{(aq)}$ (1 N, 225 mL) was added to the reaction mixture, which was then stirred for 1 h. The phases were separated and the aqueous layer was extracted with dichloroethane (2 × 100 mL). The organic layers were pooled, washed with brine (1 × 250 mL), dried over anhydrous sodium sulfate, and filtered. The solvent was removed by rotary evaporation under reduced pressure to afford the crude product as a pale yellow semisolid (92.4 g, 98%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.59−3.40 (m, 4H), 2.98−2.84 (m, 1H), 2.59−2.43 (m, 4H), 2.12−2.03 (m, 2H), 2.00−1.83 (m, 4H), 1.76−1.55 (m, 2H), 1.51−1.41 (s, 9H).

*1-Cyclobutyl[1,4]diazepane Dihydrochloride (**5·2HCl**).*[6b] A slurry of crude 4-cyclobutyl[1,4]diazepane-1-carboxylic acid *tert*-butyl ester (7) (92.4 g, 363.8 mmol) in a mixture of dioxane/MeOH (100 mL/50 mL) was treated with HCl in dioxane (250 mL, Aldrich: 4M) followed by heating to 55 °C in an oil bath. A pale orange-yellow solution resulted, and the temperature was maintained at 55 °C for 16 h. After cooling to ambient temperature, the reaction mixture was concentrated to a pasty solid. MTBE (200 mL) was added, and the slurry was agitated at

dx.doi.org/10.1021/op200005e |*Org. Process Res. Dev.* 2011, 15, 638–648

ca. 55 °C in an oil bath for 1 h. The solvent was removed by rotary evaporation under reduced pressure to afford the product as an off-white solid (81.2 g, 98%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 11.92 (s, 1H), 9.87 (s, 1H), 9.46 (s, 1H), 3.76−3.03 (m, 9H), 2.43−2.33 (m, 2H), 2.17−2.15 (m, 4H), 1.75−1.60 (m, 2H).

*(6-Chloropyridin-3-yl)(4-cyclobutyl[1,4]diazepan-1-yl)methanone (**9**).* To a flask charged with 1-cyclobutyl[1,4]diazepane dihydrochloride (**5·2HCl**) (110.0 g, 484.6 mmol), 1 N NaOH (1400 mL), and isopropyl acetate (600 mL) was added a precooled (0 °C) solution of 6-chloronicotinyl chloride (**8**) (82.7 g, 470.0 mmol) in isopropyl acetate (800 mL) via an addition funnel at a rate such that the reaction temperature was maintained between 5 and 10 °C. After the addition was complete, the reaction mixture was warmed to ambient temperature and stirred for 2 h (pH of reaction mixture ca. 5.6). The reaction mixture was basified with 2 N $NaOH_{(aq)}$ (to pH 13). The phases were separated and the aqueous layer was extracted with isopropyl acetate (2 × 300 mL). The organic layers were pooled and filtered through a pad of Celite to remove some reddish-brown flocculent material. The filtrate was washed with brine (1 × 300 mL) and dried over anhydrous sodium sulfate. Filtration and removal of the solvent by rotary evaporation under reduced pressure afforded the crude product as a reddish brown oil (126.0 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (m, 1H), 7.74 (m, 1H), 7.39 (m, 1H), 3.86−3.76 (m, 2H), 3.53−3.45 (m, 2H), 3.05−2.80 (m, 1H), 2.70 (br s, 1H), 2.62−2.45 (m 3H), 2.10−1.56 (m, 8H). MS (electrospray): calcd 293.1; *m/z* found 294.1 $[M + H]^+$.

*(4-Cyclobutyl[1,4]diazepan-1-yl)[6-(4-fluorophenoxy)pyridin-3-yl]methanone (**1**).* A suspension of anhydrous DMA (625 mL), 4-fluorophenol (57.3 g, 511.6 mmol), and Cs_2CO_3 (278.0 g, 853.3 mmol) was stirred for 15 min, and then a solution of crude (6-chloropyridin-3-yl)(4-cyclobutyl[1,4]diazepan-1-yl)methanone (**9**) (125.0 g, 426.6 mmol) in anhydrous DMA (625 mL) was added via an addition funnel over 0.5 h. The reaction mixture was heated to 100 °C and maintained at that temperature for 12 h. The reaction mixture was cooled to room temperature and filtered through a pad of Celite (3 in. Celite pad in a 600 mL coarse glass frit), then the Celite pad was washed with DMA (2 × 125 mL). The reaction mixture was diluted with a slurry of ice/water (ca. 1 L) and 2 N $NaOH_{(aq)}$ (500 mL). The pH of the reaction mixture was 13. Out of convenience, the reaction mixture was divided into two approximately equal portions. Each portion was extracted with MTBE (3 × 300 mL). The organic layers were pooled, dried over anhydrous $MgSO_4$, filtered, and concentrated by rotary evaporation under reduced pressure to afford the crude product as a thick, orange-colored oil (129 g). The oil was taken up in anhydrous diethyl ether (1 L) and stirred overnight. After removal of the resulting solids by filtration, the filtrate was concentrated to provide **1** as an orange oil (120 g, 76%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (br s, 1H), 7.79 (dd, *J* = 8.48, 2.39 Hz, 1H), 7.11−7.10 (m, 4H), 6.95 (d, *J* = 8.48 Hz, 1H), 3.76 (t, *J* = 5.84 Hz, 2H), 3.55−3.50 (m, 2H), 2.90−2.84 (m, 1H), 2.61 (t, *J* = 4.71 Hz, 1H), 2.55−2.37 (m, 3H), 2.06−1.92 (m, 3H), 1.88−1.56 (m, 5H). MS (electrospray): calcd 369.2; *m/z* found 370.1 $[M + H]^+$.

*(4-Cyclobutyl[1,4]diazepan-1-yl)[6-(4-fluorophenoxy)pyridin-3-yl]methanone Hydrochloride Monohydrate (**1·HCl·H$_2$O**).* A solution of crude (4-cyclobutyl[1,4]diazepan-1-yl)[6-(4-fluorophenoxy)pyridin-3-yl]methanone (**1**) (118.0 g, 319.8 mmol) in ethanol/diethyl ether (400 mL each) was cooled to 5 °C in an ice−water bath. Ethereal HCl (152 mL, 304 mmol, 0.95 equiv; Aldrich: 2 M solution) was added dropwise via the addition funnel. The addition was complete in 0.5 h. The reaction mixture (a suspension) was stirred for 2 h, and then diluted with diethyl ether (200 mL). The resulting suspension was stirred at ambient temperature for 16 h. The suspension was recooled to 0 °C, maintained at that temperature for 2 h with agitation, then filtered. The filter-cake was broken and washed with Et_2O/EtOH (60:40, 3 × 100 mL) and the product was dried under house vacuum for 1 h, then in a vacuum oven at 50 °C for 48 h. The product (113.5 g) was suspended in Et_2O (2 L) and agitated (mechanical stirrer) for 6 h. The suspension was filtered, then the filter-cake was broken and washed with Et_2O (3 × 100 mL). The product was dried in a vacuum oven at 45 °C for 16 h (106.8 g, 82%). ^{1}H NMR (400 MHz, D_2O) δ 8.09−8.05 (m, 1H), 7.88−7.81 (m, 1H), 7.13−7.09 (m, 4H), 7.02 (d, *J* = 8.64 Hz, 1H), 4.15−3.39 (m, 7H), 3.07−2.90 (m, 2H), 2.28−1.99 (m, 6H), 1.75−1.63 (m, 2H). ^{13}C NMR (150 MHz, D_2O) δ 2 rotamers (171.1, 170.8), (164.62, 164.55), 160.0 (d, J_{C-F} = 242 Hz), 148.8, (145.8, 145.4), (140.0, 139.7), (126.0, 125.7), 123.0 (d, J_{C-F} = 9 Hz), 116.7 (d, J_{C-F} = 23 Hz), (111.8, 111.6), 59.55, 6 carbons (51.53, 51.51, 50.6, 49.5, 48.2, 44.8, 44.7, 41.2, 26.0, 25.9, 24.2, 22.8), (12.3, 12.2). Anal. Calcd for $C_{21}H_{24}FN_3O_2 \cdot HCl \cdot H_2O$: C, 59.50; H, 6.42; N, 9.91. Found: C, 59.36; H, 6.66; N, 9.98.

Second Generation Synthesis: *Ethyl 6-(4-Fluorophenoxy)-nicotinate (**11**)* To a solution of 6-chloronicotinate (**10**) (100.00 g, 0.522 mol), and 4-fluorophenol (65.09 g, 0.575 mol) in DMF (194 mL) was added Cs_2CO_3 (189.19 g, 0.575 mol) in one portion. The reaction temperature increased from 20 to 30 °C over 10 min without external heating and then started cooling down. The resulting suspension was stirred at rt for 2−3 h and the internal reaction temperature cooled back to 23−25 °C. The reaction mixture was then heated to 60 °C and stirred for 18−20 h. HPLC analysis indicated that the reaction was complete. The heating mantle was removed and the reaction mixture was allowed to cool to 25−30 °C. To the mixture was added deionized water (146 mL) in a steady stream over 5 min and a slight exotherm was observed. The resulting suspension was stirred at rt for 15−20 min. Two additional portions of deionized water (146 mL each) were added and the suspension was stirred at rt for 15−30 min. The pH of the suspension was around 9−10. The solid product was collected by vacuum filtration, rinsed thoroughly with deionized water in portions. The filter cake was dried in a filter funnel by pulling through air for 24 h. The product was isolated as a white solid (133.6 g, 98%). Mp 68 °C (by DSC). ^{1}H NMR ($CDCl_3$) δ 8.81 (d, *J* = 2.6 Hz, 1H), 8.22 (dd, *J* = 8.5, 2.6 Hz, 1H), 7.12 (br s, 2H), 7.10 (d, *J* = 1.0 Hz, H), 6.94 (d, *J* = 8.5 Hz, 1H), 4.38 (q, *J* = 7.1 Hz, 2H), 4.38 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.3, 165.0, 159.9 (d, J_{C-F} = 244 Hz), 150.2, 149.1 (d, J_{C-F} = 3 Hz), 140.6, 123.0 (d, J_{C-F} = 8 Hz), 121.6, 116.4 (d, J_{C-F} = 24 Hz), 110.7, 61.2, 14.3.

*(1,4-Diazepan-1-yl)(6-(4-fluorophenoxy)pyridine-3-yl)methanone (**12**).* Homopiperazine (234.4 g, 2.34 mol) and ethyl 6-(4-fluorophenoxy)nicotinate (**11**) (251.34 g, 0.962 mol) in THF (2 L) were cooled to 0 °C and a solution of hexyllithium (2.3 M in hexane, 440.41 g, 1.43 mol) was added via addition funnel over 1 h. The reaction mixture was warmed to 25 °C and stirred for 2 h. The reaction was cooled to 15 °C and quenched with water (1 L). The organic layer was extracted with 600 mL of a 2 N $HCl_{(aq)}$ solution. The layers were mixed then separated, and the

organic layer was extracted with additional 2 N $HCl_{(aq)}$ (200 mL). The combined aqueous layers were allowed to sit at room temperature for 12 h. The resulting solids were removed by filtration through a glass fiber filter. The filtrate was then extracted with *tert*-butyl methyl ether (7 × 180 mL) to remove residual diamide byproduct. A solution of NaOH (50% w/w, 175.4 g, 2.19 mol) was added to the aqueous layer until a pH of greater than 10 was reached. The layers were separated and the aqueous layer was extracted with additional ethyl acetate (2 × 150 mL). The combined organic layers were then washed with brine (100 mL). Ethyl acetate (100 mL) was added to remove water through azeotropic distillation. Additional ethyl acetate (600 mL) was added in several portions and distillation was continued. The residue was filtered hot to remove sodium chloride and the filtrate was stirred for several hours until a large amount of solid had formed. The mixture was treated slowly with heptane (500 mL) over 1 h and then stirred for an additional hour. The resulting solids were isolated by filtration and dried to give the title compound as an off-white to yellow solid (168.9 g, 56%). Mp 95.4 °C (by DSC). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (dd, J = 2.4, 0.6 Hz, 1H), 7.79 (dd, J = 8.5, 2.4 Hz, 1H), 7.16−7.06 (m, 4H), 6.95 (d, J = 8.4 Hz, 1H), 3.76 (br s, 2H), 3.59−3.45 (br m, 2H), 3.12−2.84 (br m, 4H), 1.97−1.69 (br m, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 2 rotamers 168.8, 164.0, 159.8 (d, J_{C-F} = 244 Hz), 149.3, (146.1, 145.9), (139.0, 138.8), 127.7, 122.9 (d, J_{C-F} = 8 Hz), 116.4 (d, J_{C-F} = 23 Hz), 111.1, 5 carbons (52.8, 50.6, 49.5, 49.3, 48.9, 48.4, 47.8, 45.5, 31.7, 29.2). HRMS (electrospray): calcd 316.1456; m/z found 316.1453 $[M + H]^+$.

*(4-Cyclobutyl-1,4-diazepan-1-yl)(6-(4-fluorophenoxy)pyridince-3-yl)methanone Hydrochloride Monohydrate (**1**).* A suspension of (1,4-diazepan-1-yl)(6-(4-fluorophenoxy)pyridin-3-yl)methanone (**12**) (136.2 g, 428 mmol) in ethyl acetate (1.08 L) was warmed to 35 °C to dissolve all solids. The solution was cooled to 5−10 °C, cyclobutanone was added (36.33 g, 513 mmol), and the resulting mixture was stirred for an additional 10 min. Sodium triacetoxyborohydride (143.09 g, 641 mmol) was then added in several portions over 20 min. The resulting suspension was stirred at 15 °C for 15 min, and then at ambient temperature for 3 h. The reaction was quenched with a solution of potassium carbonate (164.15 g, 1.175 mol) in deionized water (540 mL). After the mixture was stirred for 30 min, the layers were separated and the organic layer was further washed with deionized water (3 × 540 mL). The organic layer was filtered through a pad of Celite (10 g) and rinsed with ethyl acetate (270 mL). The combined organic layer was assayed by HPLC to contain 143.88 g of freebase, which corresponds to a 90% crude yield. The solution was diluted with ethanol (270 mL) and a solution of concd $HCl_{(aq)}$ (36.73 g, 368 mmol, 0.95 equiv of the freebase based on HPLC assay) in ethanol (67 mL) was added slowly. The resulting solution was stirred at ambient temperature for 24 h, during which time the desired product precipitated out. The resulting solids were filtered, washed with ethyl acetate, and dried in a vacuum oven at 50 °C for 24 h. The product was then rehydrated in a sealed oven at ambient temperature in the presence of a saturated solution of $ZnSO_4 \cdot 7H_2O$ (100 g, 348 mmol) in deionized water (200 mL) for 24−48 h to form the monohydrate of the desired product as a white solid (125 g, 69%). Karl Fischer analysis: ∼4.25 wt % water. Mp 143.4 °C (by DSC).

Third Generation Synthesis: *(6-Chloropyridin-3-yl)[1,4]-diazepan-1-yl-methanone (**13**) (Method A)* Homopiperazine (33.35 g, 333 mmol) and potassium carbonate (36.8 g, 266 mmol) were suspended in *tert*-amyl alcohol (285 mL). The reaction mixture was cooled to 0 °C and 6-chloronicotinoyl chloride (**8**) (23.4 g, 133 mmol) was added as a solid over 20 min. The resulting mixture was stirred overnight at room temperature. The reaction was quenched with water (285 mL) and the layers were separated. The aqueous was extracted with additional ethyl acetate (285 mL). The combined organics were then extracted with a NaOAc/HOAc buffer (pH ∼3.74). The resulting aqueous layer was basified with a 50% $NaOH_{(aq)}$ solution until a pH of 13.4 was reached. The aqueous was then extracted with additional isopropyl acetate (3 × 500 mL) and chloroform (1 × 500 mL). The combined organics were dried over sodium sulfate, filtered, and concentrated under reduced pressure to provide the desired product **13** (11.9 g, 37% yield).

*(6-Chloropyridin-3-yl)[1,4]diazepan-1-yl-methanone (**13**) (Method B).* A solution of homopiperazine (385.62 g, 3.85 mol) in THF (3.9 L) was cooled to an internal temperature of 0 °C and ethyl 6-chloronicotinate (**10**) (285.82 g, 1.54 mol) was added in THF (0.57 L) over 5 min. After the mixture was stirred for 10 min, *n*-hexyllithium (2.3 M in hexane, 335 mL, 0.77 mol) was added over 40 min. Although the addition was exothermic, the maximum temperature was maintained at less than 5 °C. The reaction mixture was stirred for 2 h at 0 °C and then warmed to 20 °C over 1 h. The mixture was then stirred at 20 °C for 15 h, at which time HPLC analysis revealed no residual starting material. The reaction mixture was treated with 5 L of a 1 M NaOAc/HOAc buffer prepared by diluting 47.35 g of sodium acetate and 253.2 mL of acetic acid with water to a total volume of 5 L. The aqueous layer was found to contain the desired product and a reduced amount of impurity **14**, relative to the crude reaction product. The aqueous layer pH was then increased from 8.0 to 11.35 with 153 mL of 50% $NaOH_{(aq)}$ solution. The basic layer was extracted with dichloromethane (2 × 4 L) and the resulting organics dried with sodium sulfate, filtered, and concentrated to a thick oil (292.73 g crude, 87.1 wt % desired, 255.1 g actual product, 69% yield). By ^{1}H NMR, the crude reaction product was also found to contain 0.3 wt % of dichloromethane, 3.7 wt % of THF, an estimated 4.4 wt % of various impurities including **14** and **18**, and 4.5 wt % of **16**. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46−8.45 (m, 1H), 7.75−7.72 (m, 1H), 7.40−7.38 (m, 1H), 3.80−3.75 (m, 2H), 3.49−3.44 (m, 2H), 3.09−3.06 (m, 1H), 2.96−2.89 (m, 3H), 1.95−1.88 (m, 1H), 1.75−1.70 (m, 1H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 2 rotamers 167.9, (152.2, 152.1), (147.8, 147.5), (137.6, 137.3), 131.6, (124.2), 5 carbons (52.6, 50.5, 49.4, 49.3, 48.8, 48.3, 47.8, 45.4, 31.6, 29.0). HRMS (electrospray): calcd 240.0898; m/z found 240.0885 $[M + H]^+$. For impurity **16**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.79 (dd, J = 2.3, 0.6 Hz, 1H), 7.98 (dd, J = 9.0, 2.4 Hz, 1H), 6.46 (dd, J = 9.0, 0.7 Hz, 1H), 4.32 (q, J = 6.9 Hz, 2H), 3.82−3.75 (m, 4H), 3.04−3.01 (m, 2H), 2.85−2.82 (m, 2H), 1.91−1.86 (m, 2H), 1.36 (t, J = 7.1, 3H). The structure was assigned on the basis of HMBC spectrum showing ethyl CH_2 interacting with two quaternary carbons. MS (electrospray): calcd 249.2; m/z found 250.2 $[M + H]^+$.

*(6-Chloropyridin-3-yl)[1,4]diazepan-1-yl-methanone (**13**) (Method C).* Homopiperazine (12.52 g, 125 mmol) and ethyl 6-chloronicotinate (**10**) (9.28 g, 50 mmol) were taken up in tetrahydrofuran (150 mL). After the mixture was cooled to 0 °C, LiOEt (1 M in THF, 50 mL, 50 mmol) was added over 20 min. The mixture was stirred for 2 h at 0 °C and then warmed to room temperature and held overnight. To the reaction mixture was then added 162 mL of an aqueous solution containing sodium

acetate (1.53 g) and acetic acid (8.2 mL). The layers were mixed and then separated. To the organic layer was added hexanes (50 mL), and it was extracted again with 162 mL of the sodium acetate/acetic acid solution described above. The combined aqueous layers (pH 6) were made basic (pH 10) through addition of 50% $NaOH_{(aq)}$ solution (15 mL). The aqueous layer was then extracted with dichloromethane (3 × 250 mL), and the combined organics were dried over sodium sulfate and concentrated to dryness. The resulting crude oil (15.05 g) was calculated to contain approximately 72 wt % of the desired product (10.8 g, 90% crude yield). Further purification, if desired, was possible through reverse phase HPLC under basic conditions (Waters X-Bridge prep C18 5 μm 30 × 100 mm OBD column, 80 mL/min, Solvent A = 10 mM ammonium hydroxide in water, Solvent B = acetonitrile, 5% B for 2 min ramping to 99% B over 15 min). The resulting eluent was concentrated, saturated with sodium chloride, and extracted into dichloromethane (3 × 100 mL). After concentration, **13** was afforded in 67% overall yield.

*(6-Chloropyridin-3-yl)(4-cyclobutyl[1,4]diazepan-1-yl)methanone (**9**).* To a solution of (6-chloropyridin-3-yl)[1,4]-diazepan-1-ylmethanone (**13**) (from Method B above, 255.1 g, 1.06 mol; note that the starting material also contained ~53 mmol of impurity **16** from the previous step; thus total secondary amine was estimated at 1.11 mol) in dichloroethane (3.0 L) was added cyclobutanone (108.1 mL, 1.45 mol), and then the solution was allowed to stir for 1 h. Sodium triacetoxyborohydride (308.2 g, 1.45 mol) was then added in four equal portions over 1.5 h. Each addition was accompanied by an exotherm of about 4 °C. The reaction mixture was allowed to stir for 20 h and then quenched with 2.5 L of an aqueous solution containing NaOH (141.3 g, 3.53 mol). After the mixture was stirred for 30 min, the layers were separated and the organic dried with magnesium sulfate, filtered, and concentrated to provide the desired product as an oil (360.07 g crude, 86.5 wt % desired, 311.46 g actual product, quantitative yield). By ^{1}H NMR, the material was also found to contain 4.4 wt % of the reductive amination product of **16** as well as 5.6 wt % of dichloroethane, and an estimated 3.5 wt % of other impurities. The material was purified through formation of the corresponding tartrate salt as follows: Crude (6-chloropyridin-3-yl)(4-cyclobutyl[1,4]diazepam-1-yl)methanone (311.5 g actual desired, 1.06 mol) was taken up in ethanol (3.0 L). To the mixture was added L-tartaric acid (167.05 g, 1.11 mol). The heterogeneous suspension was warmed to 80 °C over 45 min and held for 1 h. The mixture was then cooled to 20 °C over 3 h and stirred at 20 °C for 1 h. The resulting solids were filtered and washed with 1 L of ethanol (Cake cracking observed—precautions must be taken to ensure efficient cake washing). The material was dried under vacuum at 43 °C to provide an off-white solid (432.52 g crude, 95 wt % desired, 411 g actual product, 87% yield). By ^{1}H NMR, the material was also found to contain 5 wt % of residual ethanol. A portion of the total tartrate salt was then free based as follows: To a 4 L Erlenmeyer was added (6-chloropyridin-3-yl)(4-cyclobutyl[1,4]diazepan-1-yl)methanone·L-tartaric acid (172 g, 386.9 mmol), *i*PrOAc (1.5 L), and 1 N $NaOH_{(aq)}$ (1.5 L). The layers were thoroughly mixed and then separated. The aqueous layer was extracted with additional *i*PrOAc (1.5 L) and the combined organic layers were dried over magnesium sulfate. After filtration and concentration, the title compound was obtained as a yellow oil (101.1 g, 89% yield for free base procedure, 77% overall yield from (6-chloropyridin-3-yl)[1,4]diazepan-1-ylmethanone). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.46−8.45 (m, 1H), 7.75−7.72 (m, 1H), 7.40−7.38 (m, 1H), 3.80−3.75 (m, 2H), 3.49−3.44 (m, 2H), 3.09−3.06 (m, 1H), 2.96−2.89 (m, 3H), 1.95−1.88 (m, 1H), 1.75−1.70 (M, 1H). ^{13}C NMR (500 MHz, $CDCl_3$) δ 2 rotamers 167.8, (152.2, 152.1), (147.8, 147.7), (137.6, 137.5), (131.6, 131.5), 124.2, (59.60, 59.58), 4 carbons (52.8, 51.9, 51.0, 50.3, 50.1, 48.8, 46.5, 45.6), (28.9, 26.8), 28.0, (13.5, 13.4). MS (electrospray): calcd 239.1; *m*/*z* found 240.1 $[M + H]^+$.

*3-[5-(4-Cyclobutyl[1,4]diazepane-1-carbonyl)pyridin-2-yloxy]benzonitrile (**2**).* To a solution of (6-chloropyridin-3-yl)(4-cyclobutyl-[1,4]diazepan-1-yl)methanone (**9**) (101.0 g, 343.8 mmol) in dimethylacetamide (1.1 L) was added Cs_2CO_3 (224 g, 687.6 mmol) and *m*-cyanophenol (81.9, 687.6 mmol). The mixture was warmed to 125 °C and stirred for 20 h. After cooling to room temperature, the reaction mixture was filtered and acetic acid (1.5 L) was added to the filtrate (Note: acetic acid is known to form an azeotrope with DMA and was added to assist in its distillation). The resulting mixture was concentrated under reduced pressure to a brown crude, which was then partitioned between MTBE (1.5 L) and 1 N $NaOH_{(aq)}$ (1.5 L). The layers were thoroughly mixed and then separated. The organic extract was dried over magnesium sulfate, filtered, and concentrated to provide the title compound as a brown oil (128.4 g, 89 wt % desired, 114.3 g actual product, 90% yield). By ^{1}H NMR, the material was also found to contain 2.5 wt % of dimethylacetamide and 8.5 wt % of *tert*-butyl methyl ether. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (s, 1H), 7.84 (dd, J = 8.4, 2.4 Hz, 1H), 7.55−7.37 (m, 4H), 7.03 (d, J = 8.4 Hz, 1H), 3.77 (m, 2H), 3.53 (m, 2H), 2.98−2.80 (m, 1H), 2.70−2.58 (m, 1H), 2.55−2.35 (m, 3H), 2.15−1.53 (m, 8H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 2 rotamers (168.5, 168.4), (162.94, 162.88), 153.8, (145.93, 145.89), (139.4, 139.2), 130.6, 128.6, 128.5, 126.3, 125.0, 118.1, 113.6, 111.7, 59.6, 3 carbons (53.1, 51.9, 51.2, 50.3, 50.2, 48.9), (46.5, 45.8), (29.0, 26.8), 28.1, 13.5.

*3-[5-(4-Cyclobutyl[1,4]diazepane-1-carbonyl)pyridin-2-yloxy]benzonitrile·HCl (**2·HCl**).* A solution of 3-[5-(4-cyclobutyl-[1,4]diazepane-1-carbonyl)pyridin-2-yloxy]benzonitrile (**2**) (114 g, 302.8 mmol) in IPA (900 mL) was warmed to 40 °C. To the resulting solution was added anhydrous HCl (5 M solution in IPA, 60.6 mL, 302.8 mmol). After the addition of seed crystals, the mixture was cooled to 35 °C and held for 2 h. After cooling to room temperature, filtering, washing with IPA (220 mL), and drying at 50 °C, the title compound was provided as an off-white crystalline solid (104.2 g, up to 99.6 wt % desired, 4000−6000 ppm residual IPA, 83% yield). Note that slight cake shrinkage was observed after removal of the wash layer. Note also, if residual chloroamido pyridine **9** persists, it may be removed by additional trituration in IPA. ^{1}H NMR (400 MHz, DMSO) δ 11.45 (br s, 1H), 8.29 (br s, 1H), 8.01 (br d, J = 7.8 Hz, 1H), 7.82−7.5 (m, 4H), 7.2 (d, J = 8.5 Hz, 1H), 4.1−3.3 (m, 7H), 3.1−2.8 (m, 2H), 2.49−2.25 (m, 3H), 2.25−1.9 (m, 3H), 1.8−1.55 (m, 2H). ^{13}C NMR (150 MHz, DMSO) δ 167.8, 162.7, 153.5, 146.2, 139.7, 131.2, 128.9, 127.6, 126.9, 125.1, 118.1, 112.4, 111.2, 58.4, 50.2, 48.7, 47.7, 40.2, 25.2, 23.5, 12.6. Anal. Calcd for $C_{22}H_{25}ClN_4O_2$: C, 63.99; H, 6.1; N, 13.57; Cl, 8.59. Found: C, 63.78; H, 6.15; N, 13.33; Cl, 8.39.

■ ASSOCIATED CONTENT

Supporting Information. ^{1}H and ^{13}C spectra for key intermediates **9**, **13**, **11**, and **12**, as well as final products **1·HCl**,

dx.doi.org/10.1021/op200005e |*Org. Process Res. Dev.* 2011, 15, 638–648

2, and **2·HCl**. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author
*E-mail: dpippel@its.jnj.com.

REFERENCES

(1) Gemkow, M. J.; Davenport, A. J.; Harich, S.; Ellenbroek, B. A.; Cesura, A.; Hallett, D. *Drug Discovery Today* **2009**, *14*, 509–515.

(2) Wijtmans, M.; Leurs, R.; de Esch, I. *Expert Opin. Invest. Drugs* **2007**, *16*, 967–985.

(3) Leurs, R.; Bakker, R. A.; Timmerman, H.; de Esch, I. J. P. *Nat. Rev. Drug Discovery* **2005**, *4*, 107–120.

(4) Celanire, S.; Wijtmans, M.; Talaga, P.; Leurs, R.; de Esch, I. J. P. *Drug Discovery Today* **2005**, *10*, 1613–1627.

(5) Bonaventure, P.; Letavic, M.; Dugovic, C.; Wilson, S.; Aluisio, L.; Pudiak, C.; Lord, B.; Mazur, C.; Kamme, F.; Nishino, S.; Carruthers, N.; Lovenberg, T. *Biochem. Pharmacol.* **2007**, *73*, 1084–1096.

(6) (a) Stocking, E. M.; Aluisio, L.; Atack, J. R.; Bonaventure, P.; Carruthers, N. I.; Dugovic, C.; Everson, A.; Fraser, I.; Jiang, X.; Leung, P.; Lord, B.; Ly, K. S.; Morton, K. L.; Nepomeceno, D.; Shah, C. R.; Shelton, J.; Soyode-Johnson, A.; Letavic, M. A. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 2755–2760. (b) Pippel, D. J.; Young, L. K.; Letavic, M. A.; Ly, K. S.; Naderi, B.; Soyode-Johnson, A.; Stocking, E. M.; Carruthers, N. I.; Mani, N. S. *J. Org. Chem.* **2010**, *75*, 4463–4471.

(7) Letavic, M. A.; Aluisio, L.; Atack, J. R.; Bonaventure, P.; Carruthers, N. I.; Dugovic, C.; Everson, A.; Feinstein, M. A.; Fraser, I. C.; Hoey, K.; Jiang, X.; Keith, J. M.; Koudriakova, T.; Leung, P.; Lord, B.; Lovenberg, T. W.; Ly, K. S.; Morton, K. L.; Motley, T.; Nepomuceno, D.; Rizzolio, M.; Rynberg, R.; Sepassi, K.; Shelton, J. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4210–4214.

(8) For a recent leading reference on this type of carbonylation, see: Lagerlund, O.; Mantel, M. L. H.; Larhed, M. *Tetrahedron* **2009**, *65*, 7646–7652.

(9) For aminocarbonylation of heteroaromatic halides see: Letavic, M. A.; Ly, K. S. *Tetrahedron Lett.* **2007**, *48*, 2339–2343.

(10) Herrmann–Beller catalyst: *trans*-di(*μ*-acetato)bis[*o*-(di-*o*-tolylphosphino)benzyl]dipalladium(II) [Registry No. 172418-32-5].

(11) Catalog prices for 5-bromo-2-fluoropyridine are typically higher than for 6-chloronicotinic acid from any given single supplier. For example, AK Scientific lists the former for $272/100 g and the latter for $50/100 g.

(12) Kovganko, N. V.; Kashkan, Zh. N. *Russ. J. Org. Chem.* **2004**, *40*, 1709–1726.

(13) (a) Zhang, J.; Dong, F.; Tong, L.; Yu, Y. Faming Zhuanli Shenqing Gongkai Shuomingshu, CN Patent 1803772, 2006, CAN 145:188729. (b) Marinak, M. J.; Simonson, J. L. U.S. Patent 4497955, 1985, CAN 102:166623.

(14) This experimental procedure has been previously documented in the form of a patent: Keith, J. M.; Letavic, M. A.; Ly, K. S.; Mani, N. S.; Mills, J. E.; Pandit, C. R.; Villani, F. J.; Zhong, H. U.S. Patent 20070281923, 2007, CAN 148:54895.

(15) Standard Sigma-Aldrich pricing: *N*-Boc-homopiperazine, $3180/mol; homopiperazine $124/mol.

(16) The reaction profile is quite clean with other possible byproducts (i.e. addition of hexyllithium to the ester) not observed to any significant extent. Simple concentration of a typical crude reaction mixture (starting with 3.8 mmol of **11**) followed by flash chromatography provides a fraction of the desired product **12** (2.26 mmol) and a fraction of the pseudodimer (0.54 mmol). As 2 mmol of **11** are incorporated into each mmol of pseudodimer, these two products account for nearly 90% of the starting **11**.

(17) For desymmetrization of the more common piperazine, see: (a) Wang, T.; Zhongxing, Z.; Meanwell, N. A. *J. Org. Chem.* **2000**, *65*, 4740–4742. (b) Chou, W.-C.; Tan, C.-W.; Chen, S.-F.; Ku, H. *J. Org. Chem.* **1998**, *63*, 10015–10017.

(18) For microwave-mediated ester to amide transformation (and leading references on ester aminolysis in general), see: Varma, R. S.; Naicker, K. P. *Tetrahedron Lett.* **1999**, *40*, 6177–6180.

(19) For aluminum-mediated ester to amide transformations, see: (a) Novak, A.; Humphreys, L. D.; Walker, M. D.; Woodward, S. *Tetrahedron Lett.* **2006**, *47*, 5767–5769. (b) Huang, P.-Q.; Zheng, X.; Deng, X.-M. *Tetrahedron Lett.* **2001**, *42*, 9039–9041. (c) Basha, A.; Lipton, M.; Weinreb, S. M. *Tetrahedron Lett.* **1977**, *48*, 4171–4174.

(20) For sodium amide reactions with esters to form *N*-aryl amides, see: (a) Walker, M. D.; Andrews, B. I.; Burton, A. J.; Humphreys, L. D.; Kelly, G.; Schilling, M. B.; Scott, P. W. *Org. Process Res. Dev.* **2010**, *14*, 108–113.(b) Wang, J.; Rosingana, M.; Discordia, R. P.; Soundararajan, N.; Polniaszek, R. *Synlett* **2001**, 1485−1487.

(21) Even without the requirement for a late stage common intermediate, the second generation synthesis was not directly applicable to **2**. The hexyllithium-mediated amide bond forming step in that case was not high yielding.

(22) The side product **16** is a structural isomer of the potential side product **18**. The assignment of **16** was made after isolation of the pure material and 2-dimensional HMBC NMR analysis (2 to 4 bond couplings), which showed that the protons on the ethyl CH_2 group are correlated to two quaternary carbons with chemical shifts of 166.18 and 113.89 ppm (the carbonyl carbon and 3-position of the pyridine ring). In the case of **18**, correlation between the ethyl CH_2 group and just one quaternary carbon would be expected (the 6-position of the pyridine ring).

(23) The *n*-hexyllithium mediated coupling of **10** and homopiperazine was also attempted in toluene and MTBE. The reaction in toluene produced more of the impurity **16**, relative to the THF case. The reaction in MTBE resulted in even more of the impurity **16** and proceeded at a retarded rate.

(24) At this point in our study, we thought that the LiOEt generated from the desired reaction would react with **10** in the absence of sufficient homopiperazine lithium amide to form the undesired **17**. We subsequently found that not to be the case.

(25) A reaction with 0.1 equiv of hexyllithium provided some **13**, but **16** was the major product.

(26) It should be noted that our failed large-scale reactions were all carefully controlled with slow addition of reagents and internal temperature monitoring.

(27) Even the most commonly employed lithium amide in organic synthesis (LDA) has demonstrated exceptionally complex properties based on solvation and aggregation, which in turn have marked effects on its reactivity: Collum, D. B.; McNeil, A. J.; Ramirez, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 3002–3017.

(28) A drawback to this approach is the fact that we currently employ methylene chloride for the extraction of the secondary amine during aqueous workup. We have not yet discovered a suitable replacement.

(29) It was also possible to utilize 2-methyl tetrahydrofuran as a solvent for this step; however, in that case, the starting material was somewhat insoluble.

(30) An alternative, less desirable polymorph was formed when the salt formation was conducted in ethanol.

(31) LiOEt was used as a 1 M solution in THF from a commercial supplier. We were unsuccessful in our attempts to use commercial solid LiOEt for these reactions. Due to competitive reaction to form **16**, reactions with substoichiometric LiOEt were not high yielding. In fact, with older bottles of LiOEt that were likely not up to titer, an "excess" of the reagent was required to avoid substantial **16** formation.

(32) Gresser, M. J.; Jencks, W. P. *J. Am. Chem. Soc.* **1977**, *99*, 6963–6970.

(33) Betts, R. L.; Hammett, L. P. *J. Am. Chem. Soc.* **1937**, *59*, 1568–1572.

(34) For other early examples, see: (a) Meade, E. M. U.S. Patent 2464094, 1949, CAN 43:22693. (b) Schurman, J. V. U.S. Patent 2863888, 1958, CAN 53:42539.