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Development of a Pilot-Plant-Scale Synthesis of an Alkylated Dihydrobenzothiadiazole *S,S*-Dioxide: Incorporation of a Late-Stage Mitsunobu Reaction†

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Abstract:

The process used to prepare a functionalized dihydrobenzothiadiazole *S,S*-dioxide on a pilot plant scale is described. Key changes to the original synthesis included: modifying S_NAr reaction conditions between a substituted aniline and 2-fluoronitrobenzene from *n*-BuLi/−78 °C to KO*t*Am/0 to 15 °C; replacement of a $NaIO_4$−$RuCl_3$ oxidizing system with bleach under phase transfer conditions; and a late-stage Mitsunobu reaction. The Mitsunobu reaction was used to prepare the penultimate intermediate and the process was telescoped forward through an *N*-Boc deprotection step that generated the active pharmaceutical ingredient. The product was efficiently extracted into the aqueous phase under acidic conditions so that the Mitsunobu byproducts could be washed away from the product with toluene. Although Mitsunobu reactions appear to be rarely used on scale, our results indicate that extraction of the API into an aqueous layer is an efficient way to separate the API from triphenylphosphineoxide and hydrazinedicarboxylate byproducts.

Introduction

The synthesis of monoamine reuptake inhibitors was an area of focused research within Wyeth.[1−4] These compounds have shown potential in the treatment and prevention of a variety of conditions and disorders that includes, but is not limited to, vasomotor symptoms (e.g., hot flashes), depressive disorders, and some pain conditions such as diabetic neuropathy and fibromyalgia. Aryl sulfamide derivatives have been particularly attractive targets, and compound **11**[3] advanced recently along with requests to deliver multikilogram quantities.

The synthesis used to prepare 25 g of aryl sulfamide **11** is shown in Scheme 1. A review of this chemistry indicated that a synthetic strategy amenable to further scale-up was in place so alternative routes to the API were not evaluated. Instead, resources were focused on optimization of the established transformations and the associated process-related work necessary to enable scale-up to a pilot plant (see Table 1). The most important step to modify was step 7, a step that involved alkylation of sulfamide **8** using a Mitsunobu reaction and *N*-Boc-(hydroxyethyl)piperazine.[5] Extensive chromatograpy was required to remove the triphenylphosphine oxide and diisopropylhydrazine dicarboxylate by products. Direct alkylation of sulfamide **8** with *N*-haloethyl derivatives of piperazine **9** could provide reaction conditions that would not require chromatography. Alkylation reactions have been a popular method for nitrogen−carbon and oxygen−carbon bond formations and in a published survey of the bulk reactions run at Pfizer between 1985 and 2002, direct alkylations of nitrogen and carbon were more common than the analogous Mitsunobu reactions.[6] Additionally, a brief survey of papers published in this journal identified multiple examples where Mitsunobu reactions were not considered as viable scale-up conditions, and alternatives were developed and used on scale.[7−14]

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Scheme 1. **Large-scale synthesis of 11**

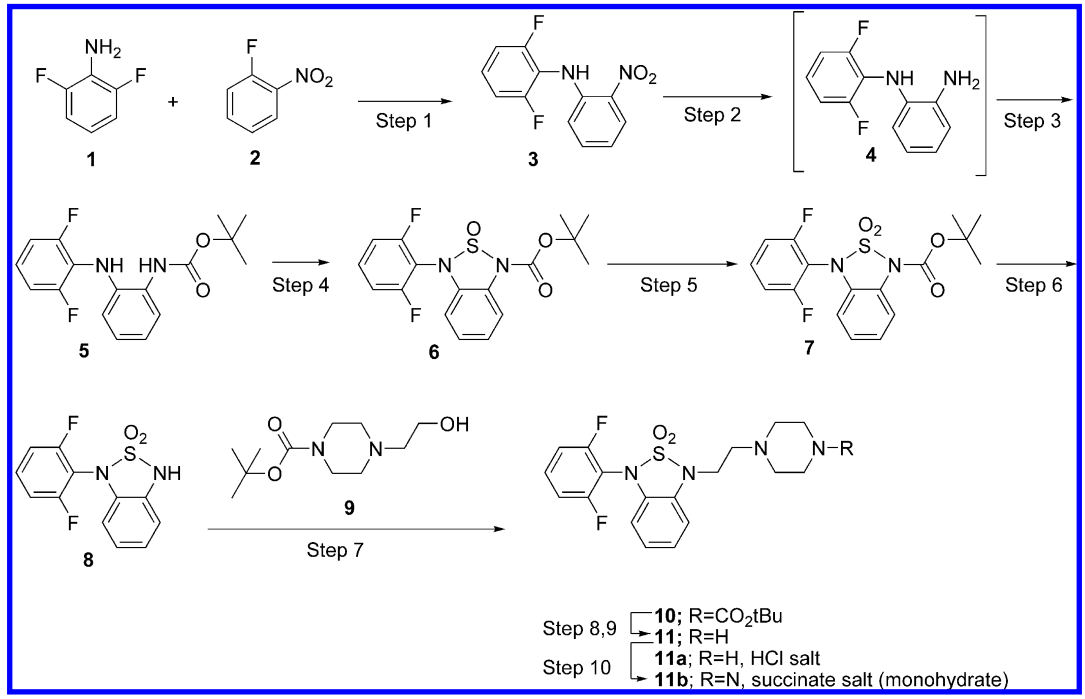

Table 1. **Comparison of original and modified reaction conditions and pilot-plant performance**

	original		modified		
step	conditions	yield (%)	conditions	lab yield (%)	plant yield (%)
1	nBuLi, THF −78 °C	63	NaO*t*Am, THF, 0−15 °C	90	92
2	10% Pd/C, EtOH, 90 psig H_2	100	10% Pd/C, THF, 40 °C, 50 psig H_2	n/a	n/a
3	Boc_2O, THF	77	Boc_2O, THF	79	96
4	$SOCl_2$/Et_3N/toluene 0−10 °C, 4 h	n/a	$SOCl_2$/Et_3N/toluene 0−10 °C, 2 h	88	93
5	$NaIO_4$, $RuCl_3$, toluene/water	n/a	$(nBu_4N)_2SO_2$, NaOCl, CH_2Cl_2	91	91
6	NaOMe, MeOH	42	NaOH, MeOH	96	99
7	diisopropylazodicarboxylate (DIPAD), PPh_3, THF, SiO2	69	DIPAD, PPh_3, THF	n/a	n/a
8	HCl, dioxane, EtOH	84	HCl, PhMe	n/a	n/a
9	n/a	n/a	NaOH, PhMe	88	79
10	n/a	n/a	succinic acid, EtOH, H_2O	90	90
overall yield (%)		12		48	58

Direct alkylation of sulfamide **8** would certainly have been more atom economical since triphenylphosphine oxide and the hydrazine byproducts would not be generated; however, the reagents required to perform the alkylation are nitrogen mustard reagents (Figure 1). *In silico* evaluation[15] indicated that piperazines **12a**−**c** were all alerting structures for being potentially genotoxic due to the presence of the haloalkane and nitrogen mustard functional groups. *In silico* evaluation of hydroxyethylpiperazine **9**, on the other hand, did not result in any such alerts. In light of the newly issued guidance on acceptable levels of potentially genotoxic impurities (PGI) in API,[16] we reasoned that the Mitsunobu reaction was worth evaluating before a decision was made to forego this transformation for an alkylation strategy. There have been reports on the successful execution of Mitsunobu reactions on scale.[17−25]

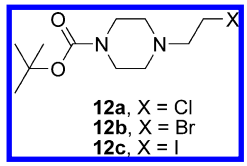

Figure 1

Results and Discussion

The first step in the sequence was a nucleophilic aromatic substitution reaction of difluoroaniline **1** with fluoronitrobenzene **2**. Although the original conditions used *n*-BuLi in THF at low temperature, we found that the displacement reaction could be achieved with alkoxide bases in THF. In fact, 3 equiv of sodium *tert*-amylate as a 35 wt % solution in THF was sufficient to function as both the solvent and the base. Both **1** and **2** were liquids, so excellent throughput was achieved by adding **1** and **2** sequentially to the cooled solution of sodium *tert*-amylate in THF.

Addition of reagents as neat liquids alerted the Scale-Up Operations group to the potential of significant exotherms since the reagents were not diluted with a solvent. However, evaluation in a reaction calorimeter (RC1) showed that the heat generated for each addition was proportional to the dose of each reagent.[26] Addition of aniline **1** resulted in a ΔT_{ad} of 3.7 °C.[27] Addition of fluoronitrobenzene **2** to the solution of NaO*t*Am and aniline **1** was significantly more exothermic (see Figure 2). The ΔT_{ad} for the reaction was determined to be 93.3 °C, however a steady heat flow of 40−50 W was observed over

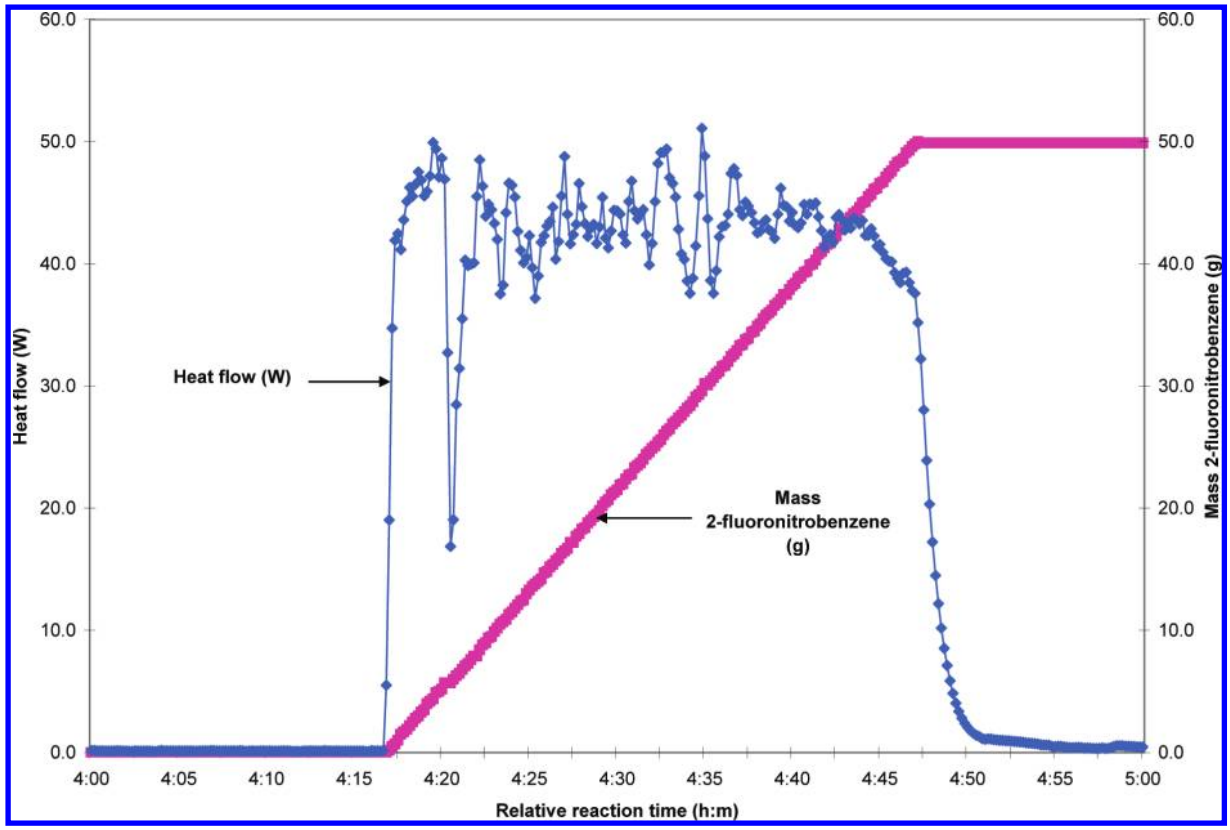

Figure 2. **Heatflow for addition of 2 to solution of 1 and NaO*t*Am in THF.**

the entire course of the addition that tapered off abruptly once the addition was complete.[28]

No temperature excursions during the addition of **1** and **2** were encountered upon scale-up; however, addition of 15.8 kg of **2** required 2 h to maintain the batch between 5 and 15 °C with the jacket set at −20 °C. Following an acidic aqueous workup and MTBE extraction, 24.4 kg of **3** was isolated from 20% aqueous 2-propanol (IPA)[29] for a yield of 92% and purity of 99.9%. Generation of HF and the potential for etching glass-lined vessels was a concern, and thus the process was run in a Hastelloy vessel. Although steps were taken to minimize contact time with glass, some etching of the glass-lined vessel that was used as a receiver during a solvent exchange and of the glass sight glass on the filter/dryer occurred.

Conversion of **3** to **5** was straightforward and easily telescoped by using THF as the solvent for the hydrogenation. A slight exotherm had been observed in the lab during the hydrogenation. When the process was scaled up to the pilot plant using 24 kg of **3**, the initial batch and jacket were both adjusted to 20 °C. As the vessel pressure was adjusted to 50 psig with hydrogen, the batch and jacket both increased to 40 °C over 90 min. These reaction conditions were held until the reaction was complete, the catalyst was then removed, and a solution of Boc_2O (1.2 equiv) in THF was added over 45 min to the solution of **4**. Following complete conversion of **4** to **5**, the solvent was exchanged to IPA via vacuum distillation to effect precipitation of **5**, and water was added as an antisolvent.[30]

(15) Wyeth used Derek for Windows, a Lhasa product, for *in silico* evaluation of genotoxicity for early-stage projects.
(16) For EMEA guidance, see: *Guideline on the Limits of Genotoxic Impurities*, CPMP/SWP/5199/02, EMEA/CHMP/QWP/251344/2006; Committee for Medicinal Products (CHMP), European Medicines Agency (EMEA): London, 28 June 2006, http://www.ema.europa.eu/pdfs/human/swp/519902en.pdf (accessed January 21, 2010).
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(26) The RC1 was operated in T_r mode so that the reactor jacket would compensate for any heat generated during the addition.
(27) Plots of T_r and T_j and Q_r as a function of dose of aniline **1** are included in the Supporting Information.
(28) The dip in heat flow that occurred at relative reaction time 4:20 occurred when dosing was momentarily paused as the reactor contents reached 10 °C, the programmed T_{max} for the addition.
(29) The solubility of **3** in 20% aq IPA was 13 mg/mL.
(30) The ambient solubility of **5** was 127, 1, 54, and 5 mg/mL in IPA, water, 80/20 IPA/water, and 50/50 IPA/water, respectively.

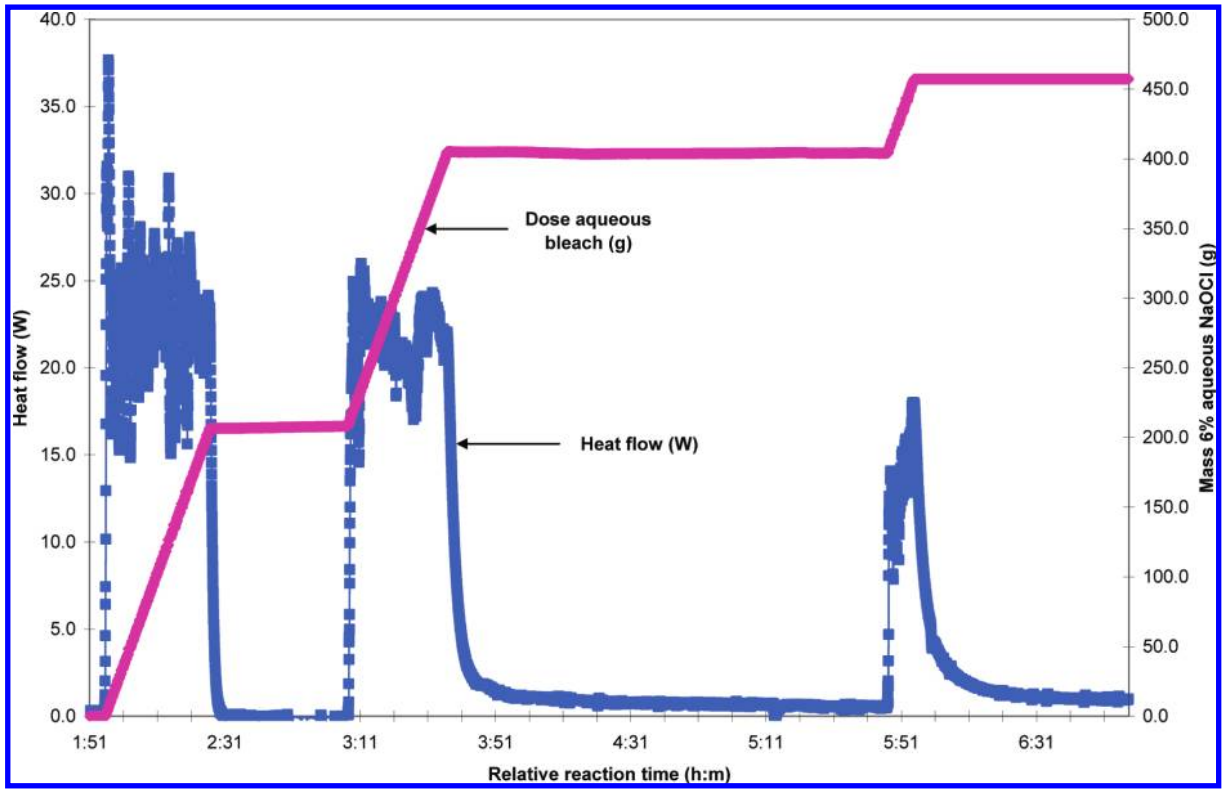

Figure 3. **Heatflow for oxidation of 6 with NaOCl.**

On scale, 29.4 kg of **5** was isolated from a 55/45 mixture of IPA/water having a purity of 99.8% for a yield of 96%.[31]

Cyclization of **5** to **6** performed as expected on the basis of previous experience in our department on related systems.[32] The process was evaluated in an RC1 and the observed heatflow was proportional to the dose of thionyl chloride. The total heat output during the addition of thionyl chloride was 88 J/g of reaction mass that corresponded to a ΔT_{ad} of 50 °C. The reaction was quenched by addition of water to the reaction mixture and the heatflow profile was consistent with an initial quench of excess reagent followed by a steady heat output indicative of a heat of dilution.[33] The ΔT_{ad} was determined to be 13 °C for the entire quench process.[34]

The original synthesis did not have a crystallization procedure at this point because the toluene stock solution of product **6** was telescoped into the oxidation. A crystallization point was easily introduced given the high room temperature solubility of **6** in the processing solvent toluene (176 mg/mL) and low solubility in heptane (4 mg/mL). Losses to the mother liquors were acceptable once the wt % of heptane in toluene was greater than 80% where the solubility of **6** was determined to be 12 mg/mL. Scale-up of this process to a pilot plant provided 28.8 kg of **6** (93% yield) with a purity of 98.5 wt %.

Moving on to the oxidation step, we were reluctant to scale the original conditions. Although the solubility of starting material **6** in toluene was excellent (176 mg/mL), the solubility of the product **7** was dramatically lower (31 mg/mL). Throughput would be low with this process given the high loading of toluene required to ensure that the product remained in solution and considering that the process was biphasic. Screening alternative solvents identified that methylene chloride would provide high product solubility (243 mg/mL) while also offering the advantages of being nonreactive and nonflammable—important considerations for an oxidation reaction. Further screening of oxidation conditions identified that aqueous bleach, in combination with the phase transfer reagent tetrabutylammonium sulfate, was effective in converting **6** to **7**. The reaction was exothermic and, given the small barrier to solvent reflux offered by methylene chloride, the oxidation was evaluated in an RC1 (Figure 3).

The square nature of the heatflow curve demonstrated that accumulation of reagent did not occur and that heat output was directly proportional to the dose of bleach. The addition was paused several times as samples were taken for in-process monitoring and to ensure that pauses in the addition would not result in the reaction stalling and bleach accumulating. The total heat output for the oxidation was 70 J/g of reaction mass, and the ΔT_{ad} was calculated to be 101 °C.[35]

(31) Product **5** was filtered on a 0.3 m^2 filter/dryer and required approximately 6 h to filter, but 22 h to dry to KF < 1% at 50 °C.

(32) Papamichelakis, M.; Lunetta, J. F.; Richard, L.; Kendall, C.; Saraiva, M. C.; Wen, X.; Paquet, V.; Daigneault, S.; Zhang, P.; Lankau, M.; Mirmehrabi, M. WO/200976502, 2009.

(33) The heatflow curve was comparable to what was published recently for the addition of water to a mixture that contained excess tosyl chloride. See: Connolly, T. J.; Considine, J. L.; Ding, Z.; Forsatz, B.; Jennings, M. N.; MacEwan, M. F.; McCoy, K. M.; Place, D. W.; Sharma, A.; Sutherland, K. *Org. Process Res. Dev.* **2010**, *14*, 459–465.

(34) See Supporting Information for the RC1 data generated during the quench of this reaction.

(35) This ΔT_{ad} was calculated using the initial reaction mass and Cp value. If the reaction mass and Cp at the end of the reaction were used in the calculation, the ΔT_{ad} dropped to 34 °C.

On the pilot plant, addition of 129 kg of 6% aqueous NaOCl required 45 min. The batch temperature was easily maintained between 5 and 20 °C with the reactor jacket set to 5 °C. When the reaction was complete, residual oxidant was quenched with sodium metabisulfite, and the product was isolated from IPA following an aqueous workup and solvent exchange. A total of 26.7 kg of **7** was isolated and represented a 91% yield. The area % and wt % purity of **7** were both excellent at 99.8%; however, the product had a slightly pink color that had not been observed in the laboratory previously. Rather than taking a sample of the product through the remaining steps to determine if there would be any impact on the quality of final prodcut, product **7** was returned to a reactor and reslurried in IPA. The product recovery was >98%, and the color of the product after reslurry was beige—more consistent with the material that had been generated in the lab.[36] Of note, the three major impurities in the solid all had the same molecular weight and retention times very close to one another, consistent with monochlorination of the product and a result of our choice of oxidant. The cumulative total of these three impurities was less than 1%.

Deprotection of **7** proceeded smoothly under basic conditions in methanol using either sodium methoxide or 50% aqueous sodium hydroxide as base. The product could be precipitated from the reaction mixture by direct addition of dilute aqueous HCl. On a 25-kg scale, 18.3 kg of **8** was isolated (99% yield) having a purity of 99.7%.[37]

As mentioned previously, we were encouraged by reports of the successful use of Mitsubobu conditions on preparative scales.[17–25] In reviewing these cases, we noted that some of the successful applications involved use in an early-stage reaction of the process where high purity product was not required,[19] was performed on scales that allowed chromatography to be an option,[21,23] or upgrade of the crude product was easily achieved by a reslurry.[24] However, there were other examples that used approaches similar to what we were proposing and relied on an acid−base extraction of product away from the Mitsunobu byproduct.[17,18,20,22,25] In our case, we planned to develop a telescoped process that combined the Mitsunobu reaction to generate **10** with *N*-Boc deprotection of **10** and hoped that at low pH, **11** could be extracted into the aqueous phase, enabling a scaleable method to separate **11** from the triphenylphosphine oxide and hydrazine dicarboxylate byproducts.[38]

Coupling of **8** and **9** proceeded smoothly in THF and generated **10** with an assay yield of 94−96%. Addition of concentrated HCl to the reaction mixture led to a mild exotherm, moderate off-gassing and complete deprotection of **10** to generate **11** with an assay yield of 96−98%. Water and toluene were added, and the organic layer was discarded as the aqueous layer was washed repeatedly with toluene until triphenylphosphine oxide was below the in-process control value. The aqueous layer was then made basic with NaOH to form free base **11**, which was extracted into isopropyl acetate (IPAC) and then isolated from IPAC/heptane. GC/MS analysis of the reaction mixture following HCl addition did indicate that ring-opening of THF had occurred; however, the levels of ring-opened product were quite low, and none of this byproduct was detected in solid **11**. Conversion of **8** to **11** occurred with yields averaging 88% when performed in the laboratory.

Coupling of **8** and **9** was evaluated in a RC1 prior to the pilot-plant batch. As shown in Figure 4, the heat flow was proportional to the dose of diisopropylazodicarboxylate (DIPAD), but not linearly proportional. The observed heat-flow pattern was the result of multiple exothermic events: addition of triphenylphosphine to DIPAD, addition of **9** to the PPh_3-DIPAD adduct with release of diisopropylhydrazinedicarboxylate then coupling of **8** to the PPh_3-**9** adduct with release of triphenylphosphine oxide. The total amount of heat generated for the DIPAD addition was 100 J/g of reaction mass that corresponded to a ΔT_{ad} of 63 °C. Given this moderate heat flow, we did not evaluate changing the order of reagent addition as a way to simplify the heat flow profile or obtain a more linear relationship between reagent dosing and heat flow.

On scale, a solution of 4.9 kg of DIPAD in 7 kg of THF was added over 40 min to a reactor that contained the remaining reagents and the reaction temperature was easily controlled between 5−10 °C. Following reaction completion, HCl was added to cleave the *N*-Boc group without any appreciable temperature or pressure rise during the deprotection stage. Two toluene washes of the aqueous layer reduced the triphenyphosphine oxide content to below 0.03 wt % by LC. Following extraction of freebase **11** into IPAC and isolation from IPAC/heptane, 6.1 kg of **11** was isolated (79% yield) with a purity of 99.85%.

API Final Form

Although **11** had been delivered as a free base to support some early preclinical studies, the free base was slightly hygroscopic as shown in Figure 5. A 1.7% gain in dry weight was observed during dynamic vapor sorption (DVS) cycling, the majority of which was gained between 0−30% relative humidity. Although the moisture was readily lost upon drying, the free base also suffered from insufficient solid state stability to support advancement as the final form of the API (see Table 2).

Various salts were prepared and screened for crystallinity, solubility and stability and the succinate salt monohydrate **11b** was chosen for further development. The monohydrate phase was not hygroscopic and it offered better stability under forced degradation conditions. Although the anhydrous succinate salt could be isolated and had acceptable thermal stability, it was converted to the monohydrate at 90% relative humidity and did not subsequently convert back to the anhydrous phase at lower relative humidity. Further, suspension of the anhydrous

(36) The product had been filtered, washed, and dried on a 0.3 m^2 filter/dryer and during the product washing stage, three additional IPA rinses were performed in an attempt to remove an observed reddish color. When the filter was discharged, it was observed that the product precipitated as large granular crystals that were covered with a reddish-brown film. Cake washes on the filter were not efficient although the reslurry did result in product that was more consistent with laboratory-quality material.

(37) Filtration of the product on a 0.25 m^2 filter/dryer required only 1.5 h; however, drying the product until the residual methanol and water were less than 0.2% each required 43 h with the jacket at 40−50 °C.

(38) The Discovery organization had attempted to prepare a dihydrochloride salt of **11** prior to the project being transferred to our group. The isolated solid had a 1.8:1 ratio of HCl to **11**, making it unsuitable for development, but providing some encouragement for us that extraction of **11** into an acidic aqueous phase was a reasonable expectation.

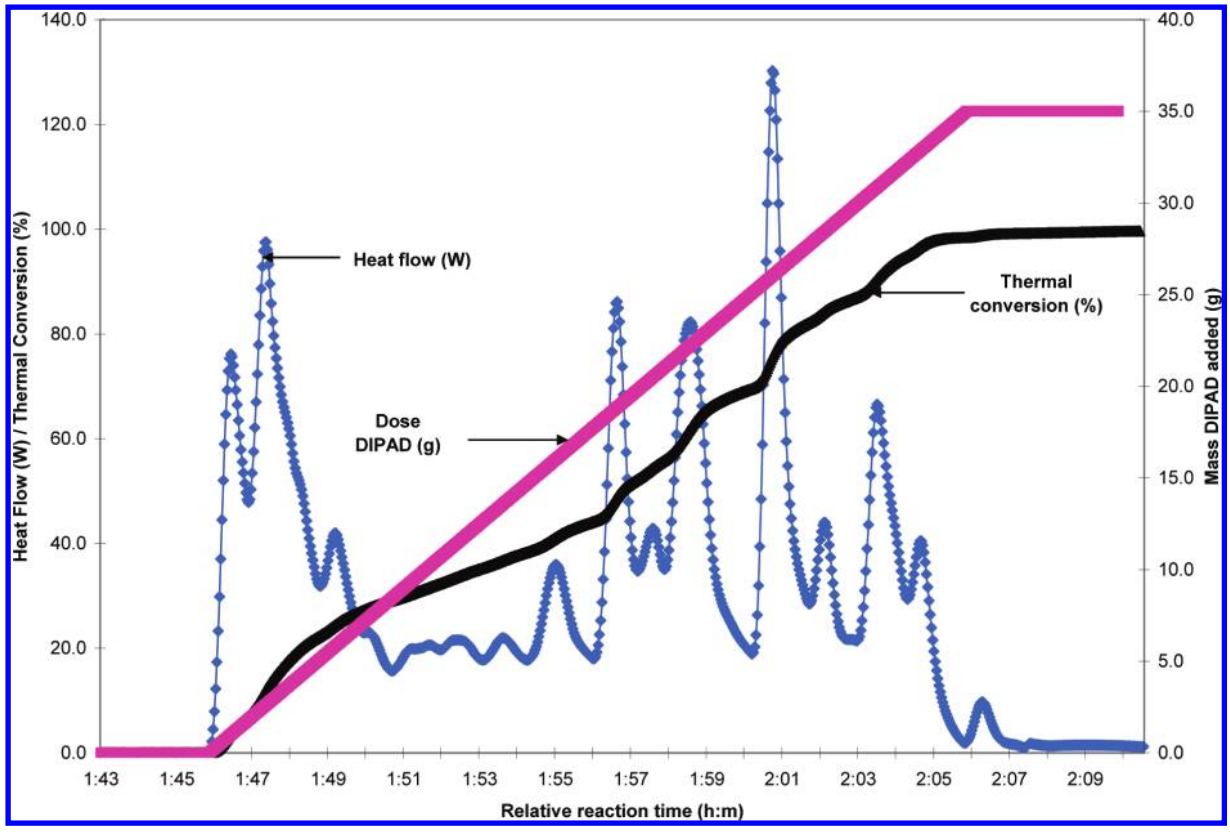

Figure 4. **Heat flow for Mitsunobu reaction.**

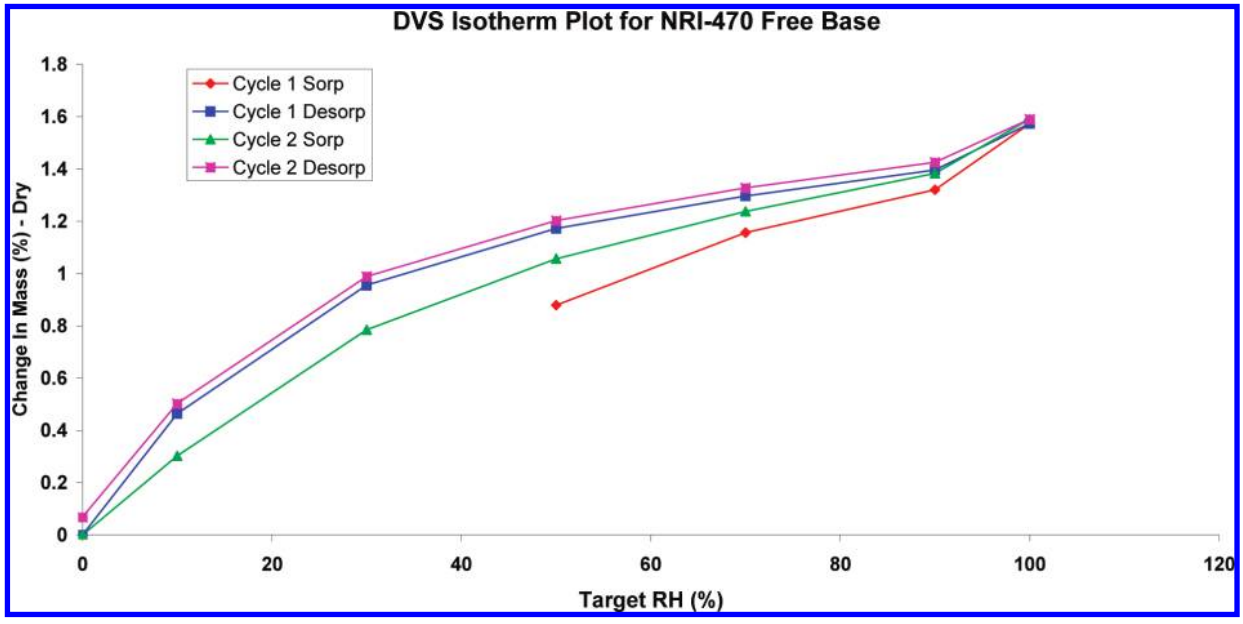

Figure 5. **DVS isotherm of freebase 11.**

succinate salt in the planned vehicle also resulted in conversion to the succinate monohydrate phase.[39] The tentative structures of the degradation products are shown in Figure 6. Forced solid-state UV degradation resulted in the formation of a compound with MW 332, proposed to be **12** and presumably the result of chelotropic expulsion of SO_2 from **11**. Forced thermal degradation of the solid API resulted in formation of a dimeric compound having MW 768 and proposed to be **13**. Not surprisingly, thermal

(39) Determined via XRD of solid.

Table 2

solid phase	UV degradation[a] (%)	hygroscopicity (%)	thermal degradation (2 weeks, 55 °C)	thermal degradation (1 day, 90 °C)
free base	3.35	1.7	0.5	17
monosuccinate, anhydrous	6.63	3.5[b]	ND	ND
monosuccinate, monohydrate	0.68	0.5	ND	ND

[a] Solid sample exposed to UV light for 20 h. [b] Converted to monosuccinate monohydrate at 90% relative humidity.

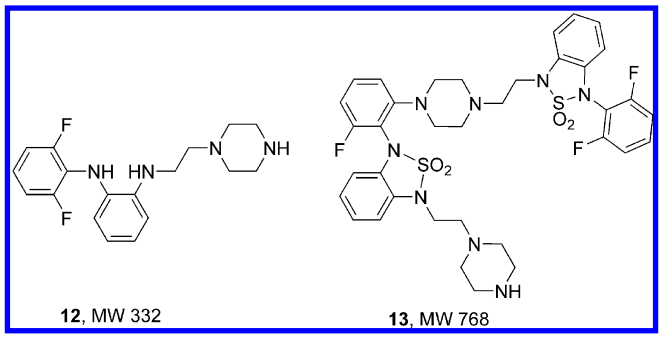

Figure 6. **Proposed API degradation products.**

Table 3. **Solubility of 11 and 11b in ethanol−water mixtures**

	solubility **11b** (mg/mL)		solubility **11** (mg/mL)	
wt % EtOH in water	23 °C	0−5 °C	23 °C	0−5 °C
0	8	−	0	0
10	12	3	1	1
30	30	13	24	3
50	50	15	>500	70
70	60	23	>500	200
80	35	−		−
90	15	4	>500	−
95	11	−		−
97	10	−		−
100	−	−	>500	170

degradation through a dimerization pathway was completely suppressed in the acid salt phases of the API.

With the succinate monohydrate selected as the desired final phase, attention shifted to development of a robust crystallization process. Ethanol−water was selected as the solvent mixture from which to isolate the desired phase and the solubilities of the starting free base phase **11** and the desired succinate monohydrate **11b** are shown in Table 3. Succinic acid was adequately soluble (>75 mg/mL) in pure ethanol, water and all compositions of the two. However, in light of the low solubility of freebase **11** in compositions of water−ethanol on the water-rich side of 50/50, we chose to evaluate the space closer to pure ethanol. When less than 3% water was present, the anhydrous phase of the succinate salt was isolated; thus, to ensure that we consistently obtained the monohydrate phase, we used 5% H_2O in ethanol as the solvent.

Addition of the free base solution *to* succinic acid was necessary to prevent formation and precipitation of a hemisuccinate phase. However, when **11b** was isolated from systems that contained excess succinic acid, the product morphology was made up of long needles that had an aspect ratio greater than 3, making it unacceptable to the formulation group. Extra heating−cooling cycles did not have a positive impact on the morphology, and thus, batch seeding was investigated as a solution.

The crystallization recipe that was ultimately developed consisted of addition of a 16.5 wt % solution of **11** in EtOH with 5 wt % H_2O at 25 °C over 2 h to a 4.27 wt % solution of succinic acid in EtOH with 5 wt % H_2O at 25 °C. Approximately 1 vol % of the batch was removed to act as seeds. The remaining reactor contents were heated to 57 °C to obtain a clear solution and then were cooled to 51 °C. The slurry of seeds was added, and the batch was held at 51 °C for 15 min then cooled to 1 °C over 10 h. The batch was held for 4 h then filtered and dried under vacuum at 50 °C, yielding **11b** with 96% yield from the free base that had a particle size distribution of $d50 \leq 29$ μm, $d90 \leq 91$ μm and an aspect ratio <3. The morphology change that occurred during this crystallization process is shown in Figure 7.

Conclusion

We have reported the synthesis of an alkylated dihydrobenzothiadiazole *S*,*S*-dioxide **11** performed on a pilot-plant scale. Of particular note in the synthesis were the development of S_NAr conditions more amenable to scale-up, mild oxidization conditions to convert dihydrobenzothiadiazole *S*-oxide **6** to *S*,*S*-dioxide **7** with commercial bleach and a phase transfer reagent and the successful utilization of a Mitsunobu reaction to form the *N*-Boc-protected API **10**. The Mitsunobu reaction and *N*-Boc deprotection were telescoped together and resulted in high-purity API that contained very low levels of triphenphosphine oxide and no reportable level of the other Mitsunobu reaction byproduct. Extraction of API **11** into aqueous acid and washing with toluene was a very efficient operation easily performed on scale. We propose that this strategy could be of use to others contemplating a late-stage alkylation strategy, especially in light of the current regulatory environment.

We have also reported on the development of a suitable salt of the API that had the required stability to enable advancement as an acceptable final form. A seeding process was developed that generated the proper morphology of the API and this process was also demonstrated on pilot-plant scale.

Experimental Section

General. Purity of each isolated solid was determined with HPLC using DAD. Two LC methods were used: Method 1 for steps 1, 2, 3 and 6: 220 nm, 35 °C, Waters Sunfire C18 column (150 × 4.6, 3 um particle size), 1.0 mL/min using a gradient method of MPA (950 mL water, 50 mL ACN, 0.5 mL TFA) and MPB (950 mL ACN, 50 mL water, 0.5 mL TFA): Initial 100%A, 50 min 0%A, 60 min 0%A, 60.1 min 100%A, 70 min 100%A. Retention times were as follows: **1** (17.36 min), **2** (21.56 min), **3** (32.16 min), **monoF-3** (32.87), **4** (15.5 min), **monoF-4** (16.43 min), **5** (35.23 min), **monoF-5** (36.28 min), 8 (22.25 min), **monoF-8** (21.81 min). Method 2: Steps 4 and 5: 220 nm, 35 °C, Phenomenex Luna, phenyl-hexyl C18 column (150 × 4.6 mm, 3 um particle size). 1.0 mL/min using a gradient method of MPA (950 mL water, 50 mL ACN, 0.5 mL TFA) and MPB (950 mL ACN, 50 mL water, 0.5 mL TFA): Initial 55% A, 20 min 45% A, 40 min 0% A, 50 min 0% A, 50.1 min 55%, 55 min 55%A. Retention times were as follows: **6** (24.86 min), **monoF-6** (24.08 min), **7** (24.4 min), **monoF-7** (24.4 min).

2,6-Difluoro-*N*-(2-nitrophenyl)aniline (3). To a 200-gal Hastelloy reactor were charged 35 wt % solution of sodium *tert*-amylate in tetrahydrofuran (101 kg, 321 mol) and THF (31.5 kg). The contents were cooled to 0−6 °C, and 2,6-difluoroaniline (15.1 kg, 117 mol) was added over 37 min at 0 to 10 °C. The batch was adjusted to 4−10 °C and stirred for 30 min. 1-Fluoro-2-nitrobenzene (14.8 kg, 105 mol) was added over 2 h (very exothermic) at <15 °C. The batch was stirred for an hour at 9−15 °C, and the reaction was checked for completion. Starting material, 1-fluoro-2-nitrobenzene, was not

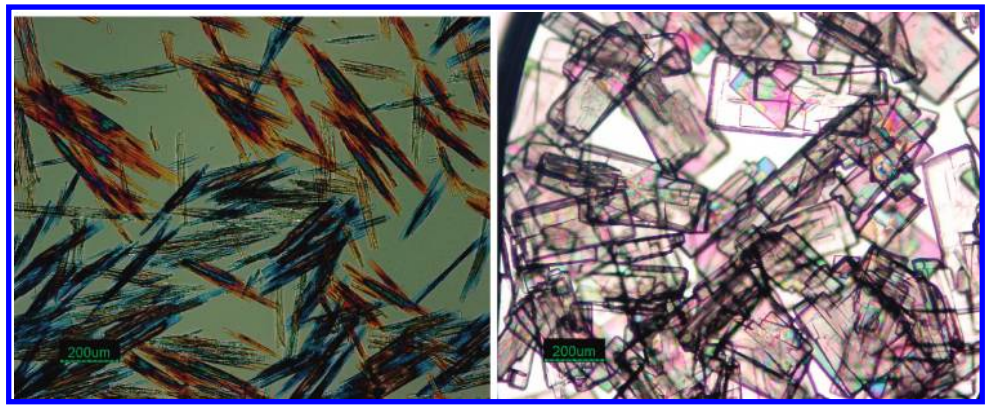

Figure 7. **View of seed slurry (left) and final slurry (right) using a polarizing microsope.**

detected by HPLC. The reaction was quenched with water (75.9 kg), followed by *tert*-butyl methyl ester (55.7 kg) and sulfuric acid (23.5 kg). The batch was adjusted to 28−34 °C, stirred for 15 min, and then allowed to settle for 45 min. The organic stream was washed with 20 wt % sodium chloride solution (86.0 kg) at 24−30 °C. The organic stream was concentrated under vacuum to 126 L (jacket temperature 60 °C, 60−80 Torr). IPA (227 kg) was added, and the batch was concentrated under vacuum to 126 L (jacket temperature 60 °C, 80 Torr). Residual THF was determined to be 0.46% (spec NMT 1%) by GC. The slurry was heated to 39−46 °C, and water (20.0 kg) was added. The batch was cooled to −10 to 0 °C over 4 h and aged for 18 h. The solids were filtered using 0.25 m^2 Rosenmund filter/dryer and washed with 24 wt % solution of IPA in water (51.9 kg) and water (63.0 kg) subsequently. The solids were dried at not more than 60 °C until LOD of 1% was achieved, total drying time 24 h. A quantity of 24.41 kg of **3** was obtained for 93% yield having LC purity of 99.9 A% (100 wt %). ^{1}HNMR (300 MHz, $CDCl_3$): δ 6.65−6.77 (m, 1H), 6.79−6.90 (m, *1*H), 6.97−7.11 (m, 2H), 7.19−7.34 (m, 1H), 7.36−7.48 (m, *1*H), 8.15−8.28 (m, 1H), 9.02 (s, broad, 1 H).

***tert*-Butyl 2-(2,6-difluorophenylamino)phenylcarbamate (5).** To a 300-gallon glass-lined carbon steel vessel were charged **3** (24.0 kg, 95.9 mol) and THF (201 kg). The mixture was cooled to below −20 °C and then transferred to an inerted 300-gal Hastelloy vessel that contained Palladium catalyst (10% on carbon 50% water-wet) (0.99 kg), rinsing forward to the hydrogenator with THF (15.0 kg). Hydrogen was introduced, and the vessel was left under hydrogen (45−55 psig, <45 °C) until the reaction was complete (2 h, 0.07% of starting material detected by HPLC). The catalyst was removed using a 12-cell Celite filter pack and washed with THF (50.7 kg). The reaction stream was transferred to 200-gal Hastelloy vessel and a solution of di-*tert*-butyldicarbonate (25.1 kg, 115 mol) in THF (66.7 kg) was added over 43 min as the reactor content was maintained at 20−30 °C. The reaction mixture was stirred for 10.5 h at ambient temperature until in-process HPLC showed 0.9% **4** remained. The reactor contents were concentrated under vacuum to a final pot volume of ∼170 L (jacket temperature 35−40 °C, ∼60−70 Torr). 2-Propanol (375 kg) was added, and the concentration under vacuum to ∼170 L was repeated (jacket temp 50 °C, 40−50 Torr, 1% THF by GC). Water (65.3 kg) was added at 44−50 °C over 80 min. The batch was cooled 26−32 °C (crystallization observed) and water (65.3 kg) was added over 30 min. The slurry was cooled to 0−6 °C over ∼3 h and filtered using a nutche filter. The cake was washed with cold 44.5 wt % 2-propanol in water solution (60.0 kg). The solids were dried at not more than 50 °C until LOD of 0.1% was achieved, total drying time ∼22 h. A quantity of 29.35 kg of **5** was obtained for 96% yield having LC purity of 99.83 area % (101 wt %). ^{1}HNMR (300 MHz, $CDCl_3$): δ 1.48 (s, 9H), 6.59 (d, J = 7.4 Hz, 1H), 6.87 (t, J = 7.4 Hz, 1H), 6.97 (t, J = 7.4 Hz, 1H), 7.04−7.26 (m, 3H), 7.41 (d, J = 7.5 Hz, 1H).

1-(*tert*-Butylcarbonyl)-3-(2,6-difluorophenyl)-1,3-dihydrobenzothiadiazole-*S*-oxide (6). To a 100-gal glass-lined carbon steel vessel was charged **5** (27.0 kg, 84.3 mol), toluene (204 kg), and triethylamine (21.3 kg, 210 mol), and the contents were cooled to −6 to 0 °C. Thionyl chloride (12.0 kg, 101 mol) was added over 1 h 40 min at −6 to 10 °C. The batch was warmed to 2−8 °C and stirred for 1 h. The reaction completion check indicated 21% of starting material by HPLC.[40] Additional triethylamine (5.3 kg, 52.4 mol) and thionyl chloride (3.0 kg, 25.2 mol) were added, and the reaction mixture was stirred at 2−8 °C for an additional 60 min. The reaction completion check indicated 0.6% of starting material by HPLC. The reaction was quenched with water (174 kg) at 2−20 °C added over 35 min and then clarified, and the phases were allowed to separate over 60 min. The upper organic phase was washed with 5 wt % sodium bicarbonate aqueous solution (154.5 kg), and the organic stream was concentrated under vacuum to a final volume of 76 L (batch temp 40−50 °C, jacket temp 60 °C, 60 Torr). Heptane (198 kg) was added, and the batch was concentrated under vacuum to a final volume of 192 L (batch temp 40−50 °C, jacket temp 50−60 °C, 100−120 Torr). Heptane (80.0 kg) was added to the slurry at 40−50 °C, in-process testing indicated 11.7% of toluene by GC. The slurry was cooled to −6 to 0 °C over 2 h, aged for 1 h, and filtered using 0.3 m^2 Nutsche filter. The cake was washed with cold 12.5 wt % toluene in heptane solution (34.7 kg). The solids were dried at not more than 50 °C until LOD of 0% was achieved; total drying time was ∼13 h. A quantity of 28.75 kg of **6** was obtained for 93% yield having purity of 99.6 area %, 98.5 wt %. ^{1}HNMR (300 MHz,

(40) The thionyl chloride used for this process was >4 years old and was not tested for potency prior to use. Release was based on the vendor CofA. Lab-scale experiments used 1.2 equiv of thionyl chloride and were always complete at this point.

$CDCl_3$): δ 1.65 (s, 9H), 6.55 (m, 1H), 7.02−7.17 (m, 4H), 7.40−7.52 (m, 1H), 7.83−7.96 (s, *broad 1*H).

1-(*tert*-Butylcarbonyl)-3-(2,6-difluorophenyl)-1,3-dihydrobenzothiadiazole-*S*,*S*-dioxide (7). To a 100-gal glass-lined carbon steel vessel was charged **6** (28.0 kg, 76.4 mol), methylene chloride (156 kg), tetrabutylammonium sulfate 50% solution in water (4.5 kg), and water (2.0 kg, rinse), and the contents were adjusted to 10−16 °C. A 6.15% solution of sodium hypochlorite was prepared by adding water (67.2 kg) to 12.8% sodium hypochlorite solution (62.2 kg, 107 mol), cooled to 10 to 16 °C, transferred to the substrate mixture over 45 min at 10−30 °C, and rinsed with water (10 kg). The batch was stirred at 20−26 °C for 37 min. Starting material was not detected by HPLC. The reaction was quenched with 10% sodium metabisulfite solution (42.0 kg) and tested for chlorine using starch iodide paper (none detected). The phases were allowed to separate at 26−32 °C over 16 min. The upper aqueous phase was washed with methylene chloride (74.2 kg), and the combined organic streams were washed with water (84.0 kg) at 22−28 °C. The batch was concentrated to 84 L (batch temp 40 °C, jacket 50 °C, atmospheric pressure). 2-Propanol (90.0 kg) was added, and the batch was concentrated to 84 L (batch temp ∼30 °C, jacket 55 °C, atmospheric pressure, 0.27% methylene chloride by GC). The slurry was cooled to 0−6 °C over 85 min, aged for 60 min, filtered using 0.3 m^2 Nutsche filter, and washed with cold 2-propanol (45.1 kg). Additional 2-propanol washes (65.0 kg) were performed to remove undesired color. The solids were dried at not more than 45 °C until LOD of 0.1% was achieved, total drying time ∼18 h. A quantity of 26.65 kg of **7** was obtained for 91% yield. The isolated product did not have a homogeneous appearance/color, so it was washed using the following procedure. Crude **7** (26.0 kg) was slurried in 2-propanol (104 kg) and stirred for 30 min at 17−23 °C and then filtered using a 0.3 m^2 Nutsche filter. The filtrate was washed with 2-propanol (2 × 20.0 kg) and dried at not more than 45 °C until LOD of 0.2% was achieved, total drying time ∼10 h. A quantity of 25.50 kg of **7** was obtained for 98% recovery having a purity of 99.8% (area % LC), 99.8% (wt % LC). ^{1}HNMR (300 MHz, DMSO): δ 1.65 (s, 9H), 6.45−6.53 (m, 1H), 7.00−7.19 (m, 4H), 7.46−7.59 (m,1H), 7.83−7.93 (m, 1H), ^{19}F NMR ($CDCl_3$): δ −114 (s, 2F).

1-(2,6-Difluorophenyl)-1,3-dihydrobenzothiadiazole-S,S-dioxide (8). Compound **7** (25.0 kg, 65.4 mol) was charged to a 100-gal glass-lined carbon steel vessel along with methanol (79.0 kg) and stirred at 20 to 26 °C for 10 min. Sodium hydroxide 50% solution (w/w) (10.5 kg) was charged over 30 min at 20 to 30 °C and stirred for 1 h at 20 to 26 °C. Starting material was not detected by HPLC. The reaction was quenched with hydrochloric acid solution (prepared from concentrated Hydrochloric Acid (16.8 kg) and water (200 kg)) and the product precipitated (final pH = 1). The slurry was cooled to 0 to 6 °C over 90 min, aged for 30 min, filtered using 0.25 m^2 Rosenmund filter, and washed with cold 33% methanol in water solution (w/w) (68.5 kg). The solids were dried at not more than 50 °C until LOD of 0% was achieved and residual methanol was 0.01% by GC. A quantity of 18.26 kg of **8** was obtained for 99% yield having purity 99.7% (area % LC), 103% (wt % LC). ^{1}HNMR (300 MHz, $CDCl_3$): δ 6.44−6.53 (m, 1 H), 6.95−7.18 (m, 6 H), 7.45−7.57 (m, 1 H).

1-(2,6-Difluorophenyl)-1,3-dihydro-3-[2-(1-piperazinyl-)ethyl]-benzothiadiazole-S,S-dioxide (11). To a 50-gal glass-lined vessel was charged **8** (5.5 kg, 19.48 mol), triphenyl phosphine (6.39 kg, 24.36 mol), 1-Boc-4-(2-hydroxyethyl)piperazine (5.39 kg, 23.40 mol) and tetrahydrofuran (41.2 kg), and the contents were adjusted to −5 to 1 °C. A solution of diisopropylazodicarboxylate (4.90 kg, 24.23 mol) in tetrahydrofuran (7.5 kg) was added over 41 min, rinsed with tetrahydrofuran (5.0 kg), stirred at 20 to 26 °C for 1 h, and sampled (2.7% of starting material by HPLC). Hydrochloric acid (11.5 kg) was added, and the batch was heated to 52−58 °C and stirred for 45 min. HPLC in-process control indicated 0.29% of Boc-protected intermediate **10** present. The contents of the batch were cooled to ambient and toluene (41.8 kg) and water (28.1 kg) were added. The mixture was stirred for 10 min and phases were allowed to separate over 1 h. The lower aqueous product stream was washed with toluene (85.3 kg) (3% of triphenylphosphine oxide was detected in the aqueous product stream). Isopropyl acetate (79.6 kg) was added and the batch was cooled to 10 to 16 °C. Sodium hydroxide 50% solution (w/w) (8.10 kg) was added and the temperature was adjusted to 14 to 20 °C. The phases were allowed to separate over 40 min, the upper organic product stream was washed with water (38.6 kg) and concentrated under vacuum to ∼18 L (batch temp. ∼15−20 °C, jacket ∼40 °C, ∼55 Torr). Heptane (17.6 kg) was added to the slurry, the batch was cooled to −5 to 5 °C, and then warmed to 20−26 °C in order to dislodge solids from the walls, recooled 0 to 10 °C, aged for 3 h, filtered using a 0.2 m^2 Rosemund filter, and washed with cold 38.8% w/w isopropyl acetate solution in heptane (9.45 kg). The free base was dried at not more than 40 °C until LOD of 0% (total drying time 17 h). A quantity of 6.1 kg of **11** was obtained for 79% yield having purity of 99.8% (area % LC), with 0.07% triphenylphosphine oxide. ^{1}HNMR (300 MHz, $CDCl_3$): δ 1.66 (s, broad, NH), 2.56 (t, J = 4.7 Hz, 4H), 2.84 (t, J = 7.3 Hz, 2H), 2.91 (t, J = 4.7 Hz, 4H), 3.94 (t, J = 7.3 Hz, 2H), 6.46 (d, J = 7.8 Hz, 1H), 6.88−6.96 (m, 2 H), 7.0−7.16 (m, 3 H), 7.44−7.56 (m, 1 H); $_{19}$F NMR ($CDCl^3$): δ −114 (s, 2F).

1-(2,6-Difluorophenyl)-1,3-dihydro-3-[2-(1-piperazinyl-)ethyl]-benzothiadiazole-S,S-dioxide Succinate Monohydrate (11b). Free base **11** (6.20 kg), ethyl alcohol (USP, 37.0 kg), and water (2.35 kg) were charged to a 50-gal Hastelloy vessel. A solution of succinic acid (1.85 kg), water (2.05 kg), and ethyl alcohol (USP, 39.4 kg) was prepared and adjusted to 22−28 °C. The free base solution was added to the solution of succinic acid in portions until crystallization was observed.[41] A seeding sample was taken from the reactor, the remaining free base solution was added, and the free base reactor was rinsed forward with ethyl alcohol (USP, 2.5 kg). The reactor contents were heated to 54−60 °C, and the resulting clear solution was cooled to 47−53 °C, and seeded; then cooled to −2 to 4 °C over 10 h, aged for 4 h, and filtered using 0.2 m^2 Rosemund filter. The cake was washed with cold 5% w/w ethyl alcohol (USP) solution in water (16.1 kg), then dried at not more than 40 °C

(41) About 75% (volume) of the free base solution was added. The batch had to be cooled to 10−18 °C before crystallization was observed.

until LOD of 0.2% (total drying time 8 h, residual solvent by GC: ethanol 276 ppm, toluene 4 ppm, THF 10 ppm, heptane 6 ppm, IPAC 12 ppm). A total of 7.5 kg of **11b** was obtained for 90% yield (for salt formation only) having purity 99.93% (area % LC) with one impurity at 0.07%.[42]

Acknowledgment

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Supporting Information Available

RC1 data for the aniline addition in step 1, thionyl chloride addition, and water quench in step 4. This material is available free of charge via the Internet at http://pubs.acs.org.

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(42) This impurity was identified as the monofluoro derivative of **11**, formed during the step 2 hydrogenation. Although six isolations had occurred between the hydrogenation stage and isolation of the API, this impurity was very resistent to purging due to its structural similarity to that of the API.