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ARTICLE

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Chemical Development of the Casein Kinase I - Epsilon Inhibitor: 3-(3-Fluorophenyl)sulfanyl-1*H*-pyrrolo[3,2-*b*]pyridine-2-carboxylic Acid Amide

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ABSTRACT: The development of a scalable process for 3-arylsulfanyl-1*H*-pyrrolo[3,2-*b*]pyridine-2-carboxylic acid amides (**1**), potent casein kinase I inhibitors, is described. The rapid identification of suitable reaction conditions expedited the lab scale synthesis of drug substances for early toxicological evaluations. Further improvements were made to achieve a safe and cost-effective process to meet increasing demands for drug substances to support clinical studies. This paper describes the synthesis at multikilogram scale.

INTRODUCTION

Casein kinase Iε, one of the isoforms of protein kinases, acts in a molecular pathway that regulates the circadian rhythm.[1] Following the discovery of the casein kinase I inhibitors, 3-arylsulfanyl-1*H*-pyrrolo[3,2-*b*]pyridine-2-carboxylic acid amides **1a,b** (Scheme 1), and their potential use for the treatment of depression,[2] multikilo quantities were required for pharmacological profiling and clinical trials. This led to the search for a safe, high-yielding, and reliable process.

DISCUSSION

The Discovery chemistry route (Scheme 1) involved a Suzuki coupling of the commercially available 2-chloro-3-nitropyridine with methylboronic acid[3] followed by alkylation of the carbanion of **2** with diethyl oxalate to provide the ketoester **3**. Reductive cyclization of the ketoester via catalytic hydrogenation led to the backbone of 4-azaindole. The sequential amidation and thioalkylation of the azaindole ester **4** gave the drug substance **1a** or **1b**.

The Suzuki coupling suffered from a modest yield, low reproducibility, and a long reaction time as well as costly reagents. An undesired chromatographic purification was also used for the product purification. Step 2 was very sluggish taking up to 3 days. The amidation required a pressure reactor and suffered a slow conversion. The final step required a long reaction time at 100 °C and subsequent chromatographic purification.

The first aim was to provide workable conditions that could be used on a large lab scale (e.g., multihundred grams) with relative ease of processing, in reasonable yield, and in a short time frame. The second target was to ensure that further scale-up in the pilot plant was achieved at multikilogram scale.

Development of Ring Methylation Process (Step 1). Several alternative cross-coupling conditions were briefly examined using Me_3Al,[4] MeMgCl,[5] and trimethylboroxine,[6] but none provided a yield greater than 40%. Direct coupling of 2-chloro-3-nitropyridine with ethyl pyruvate gave **3** in a modest yield (<50%),[7,8] and the need to use an expensive ligand, 2-dicyclohexylphosphino-2′-(*N*,*N*-dimethylamino)biphenyl, made the method less attractive.

Our attention focused on an indirect approach to introduce the methyl group. Reaction of 2-chloro-3-nitropyridine with diethyl sodiomalonate followed by decarboxylation was reported to provide 2-methyl-3-nitropyridine in 63% yield after vacuum distillation.[9] The procedure used to prepare diethyl sodiomalonate required heating sodium metal in diethyl malonate at 120 °C and was not feasible for scale-up. A process with a better safety profile was developed using diethyl malonate and a base (Scheme 2). After a base screening, including potassium *tert*-butoxide, sodium *tert*-butoxide, sodium hydride, sodium ethoxide, and sodium bis(trimethylsilyl)amide (NaHMDS), sodium *tert*-butoxide was selected. *N*-Methylpyrrolidinone (NMP) was determined to be the superior solvent as it enhanced the solubility of the base and accelerated the reaction. Excess diethyl malonate (2.0 equiv) was required to suppress formation of the bis-arylation byproduct **7**. Upon completion of the arylation in NMP at 50 °C after 2 h, the resulting **6** was decarboxylated by treatment with aqueous sulfuric acid at 100 °C for 12 h to complete a one-pot process. The product was extracted with toluene, and the toluene solution was evaporated *in vacuo* to provide **2** as an oil. The process was carried out at ca. 500 g scale to produce 2-methyl-3-nitropyridine in 80% yield.

At pilot plant scale, the product was prepared as a concentrated toluene solution (*vide infra*). The toluene was partially distilled off at a pot temperature up to 90 °C and a vacuum of 100 Torr. Compound **2** was thermally stable (decomposition temperature: 263 °C by DSC) under the distillation conditions. The process was performed in the pilot plant at 8.75 kg scale, affording **2** as a toluene solution (~60 wt %) in 90% yield.

Development of Oxalate Condensation (Step 2). A solvent screen determined that the reaction in THF was much faster than in ethanol (2 h vs 3 d). The reaction outcome was highly dependent on the order of addition. Addition of diethyl oxalate to a mixture of sodium ethoxide and **2**, or addition of sodium ethoxide to a mixture of diethyl oxalate and **2**, resulted in

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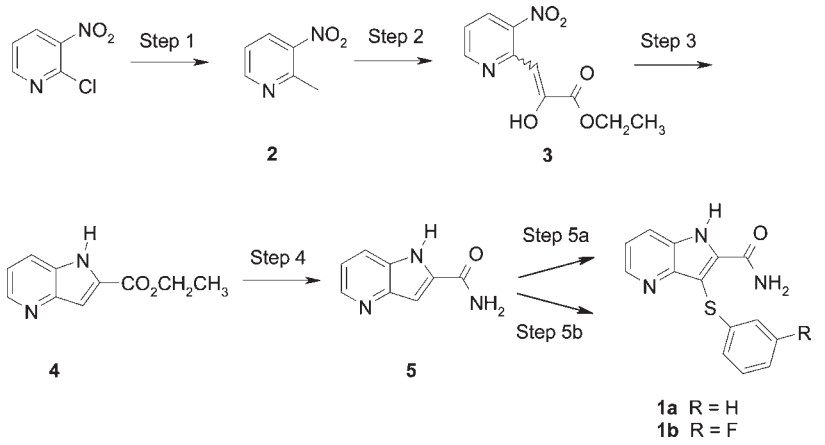
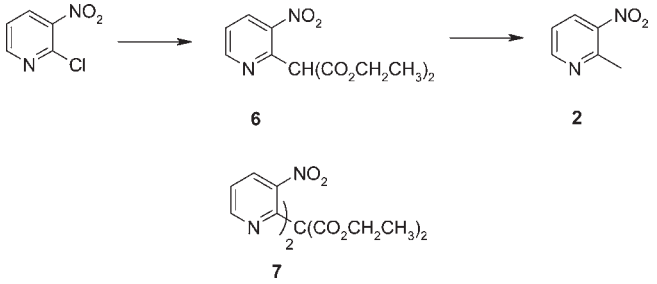
Scheme 1. Discovery route to 4-azaindole amides 1a,b[a]

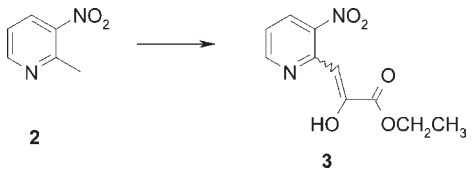


[a] *Reagents and conditions*: Step 1. $MeB(OH)_2$, K_2CO_3, $Pd(PPh_3)_4$ (10 mol %), dioxane, 100 °C, 2−3 d, 57% after chromatography; Step 2. diethyl oxalate, NaOEt, EtOH, rt, 3 d, 64%; Step 3. Pd/C, H_2 (53 psi), EtOH, rt, 4 h, 89%; Step 4. NH_3 in MeOH, rt, 3 d, 86%; Step 5. for **1a**: diphenyl disulfide, Cs_2CO_3, DMF, 100 °C, 2 d, 60% after chromatography; for **1b**: bis(3-fluorophenyl) disulfide, Cs_2CO_3, DMF, 100 °C, 20 h, 68% after chromatography. *Scale*: 0.1−10 g. Overall yield: 16.8%.

Scheme 2. Preparation of 2-methyl-3-nitropyridine via malonate intermediate 6



Scheme 3. Preparation of ketoester 3



formation of a significant amount (>10%) of undesired dimeric product. A large exotherm was generated when mixing diethyl oxalate with sodium ethoxide, which could be the cause for the dimer formation. For optimal results, it was essential to dose **2** to a premixed solution of diethyl oxalate (3.0 equiv) and sodium ethoxide (2.0 equiv) in THF at 4 °C. The resulting mixture was then warmed to room temperature and held for 2 h. Upon treatment with aqueous ammonium chloride, the ketoester **3** was isolated by vacuum filtration in 88% yield. The oxalic acid byproduct, resulting from excess diethyl oxalate, was removed with a water slurry. The procedure was used in the lab to prepare over 600 g of the ketoester **3** (Scheme 3).

On a multikilogram scale run, **2** was prepared as a toluene solution to avoid vacuum distillation to dryness. The concentration

Table 1. Effect of concentration of 2 in toluene on ketoester formation

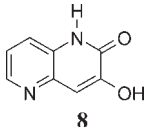
Batch Size	Wt % of **2** in toluene	Isolated Yields (%)	Purity (Area% by HPLC)
31 g	34%	82%[a]	99.2%
24 g	52%	94%	99.6%
24 g	70%	91%	98.6%

[a] 18.6% remaining starting material.

of **2** in the toluene solution affected the rate of the reaction as well as the isolated yield (Table 1). While a dilute solution (34 wt %) gave a relatively lower conversion, a concentrated solution (70 wt %) afforded a product with a slightly lower purity. A moderate concentration (ca. 50 wt %) was deemed to provide the optimal results.

Oxalic acid, coprecipitated out with **3**, was shown to slow down filtration and inhibited initiation of subsequent transfer hydrogenation. This was overcome by ensuring that a sufficient amount of water and isopropyl alcohol was used to wash the filter cake. The process was performed in the plant at 9 kg scale in 84% yield and a purity of 96.5 wt %.

Development of Pyrrole Ring Cyclization (Step 3). The original catalytic hydrogenation conditions were used for the lab preparation. A strong exotherm with an adiabatic temperature rise of 32 °C was observed during the initial hydrogen uptake at 57 g scale. After the exotherm subsided, the mixture was held to 40 °C to progress to completion. The crude product, containing ca. 2% of a six-membered ring byproduct **8**,[10] was reslurried in a mixture of ethyl acetate and heptane at reflux, giving **4** in >90% recovery (<0.2% impurity **8**). The process was used in the lab to prepare 640 g of **4**.



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The catalytic hydrogenation was used for the quick lab batch delivery, but the process was not amenable for further scale-up

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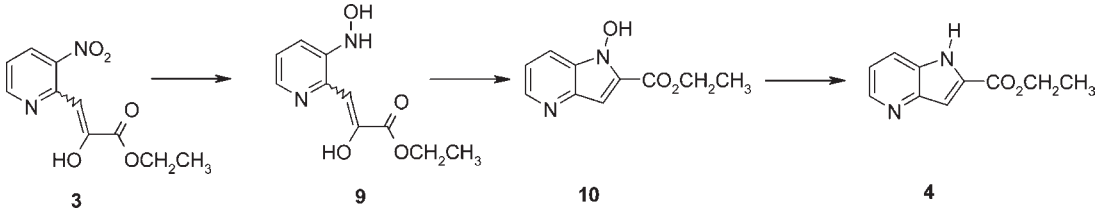
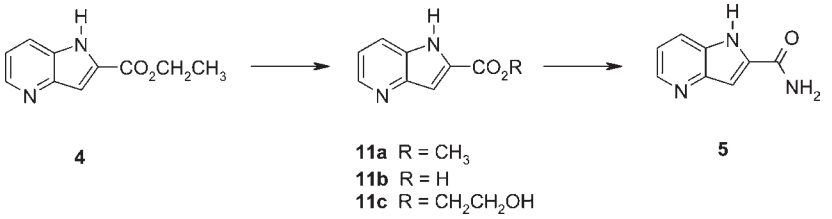
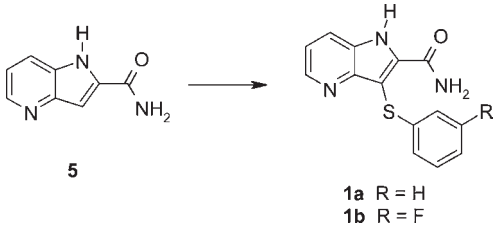
Scheme 4. Intermediates to the azaindole ester 4



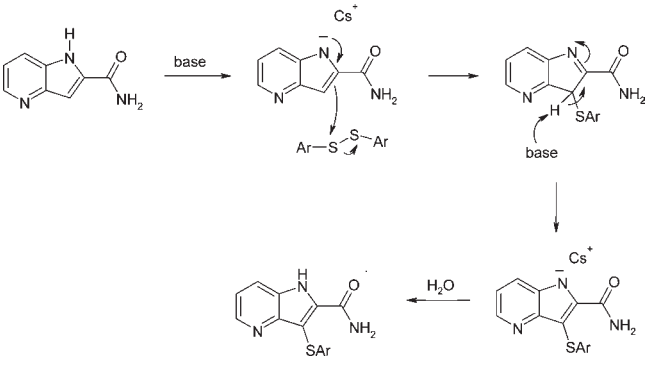
Scheme 5. Intermediates and byproducts observed in the amidation reaction



Scheme 6. Thioalkylation of azaindole amide 5



Scheme 7. Proposed mechanism for thiophenyl addition



due to pilot plant limitations at that time. Effort was then focused on the development of a transfer hydrogenation to achieve the desired transformation. The reaction was believed to proceed through intermediate **9** and cyclized hydroxylamine **10** as observed by following the reaction closely with HPLC and LCMS (Scheme 4).

Ammonium formate, formic acid, and ammonium formate with acetic acid were examined as hydrogen donors. The reaction with formic acid alone was relatively slow (<10% after 2 h). Attention was next turned to the ammonium formate−acetic acid system. The rate of reaction was shown to be comparable to ammonium formate by itself, and the acetic acid minimized the amount of sublimate. An attempt was made to perform the reaction with Pd/C and ammonium formate in the absence of acetic acid, with the hope that at a lower temperature (35 °C) the ammonium salt byproduct would not sublime. Also, eliminating acetic acid might simplify the workup by avoiding the need for neutralization. Upon completion of the reaction (pH = 8−9), a significant amount of ammonium salt sublimate had still formed on the reactor walls and at the bottom of the condenser. This led to a decision to use the ammonium formate−acetic acid process.

While working on the development of this step, it became apparent that the conditions required for the initiation of the transfer hydrogenation were dependent on the quality of the ketoester **3** used. The reaction using one particular batch of ketoester (containing 3.2 wt % of oxalic acid) did not initiate at all under the standard conditions, where the pH of the mixture was lower than that for reactions that successfully initiated. In light of the performance variability observed for various lots of the ketoester, an additional 10% of the ammonium formate solution was charged to ensure a smooth initiation of the reaction. The catalytic decomposition of ammonium formate resulted in a pH increase that might help solubilize the oxalic acid.

Two lab batches (25 and 65 g) were carried out using the final process, providing **4** in 80−87% yield.

The process was transferred to the pilot plant, and four batches at 8 kg scale were completed. The reaction and workup proceeded satisfactorily, in good agreement with the observations in the lab. A total of 22.1 kg of **4** were produced in 86.9−89.9% yield.

Development of Amidation (Step 4). The amidation was initially performed with a solution of ammonia in methanol taking 3 d to complete at room temperature. To improve the rate of conversion, the reaction was carried out at 50 °C with less MeOH (15 parts) and was complete in 36 h. The reaction mixture started as a suspension that dissolved on heating, and the product precipitated upon cooling. The mixture was filtered and washed with methyl *tert*-butyl ether to provide **5** in 90−95% yield. The reaction in methanol proceeded through a trans-esterification to the methyl ester **11a**; thus the impurities observed

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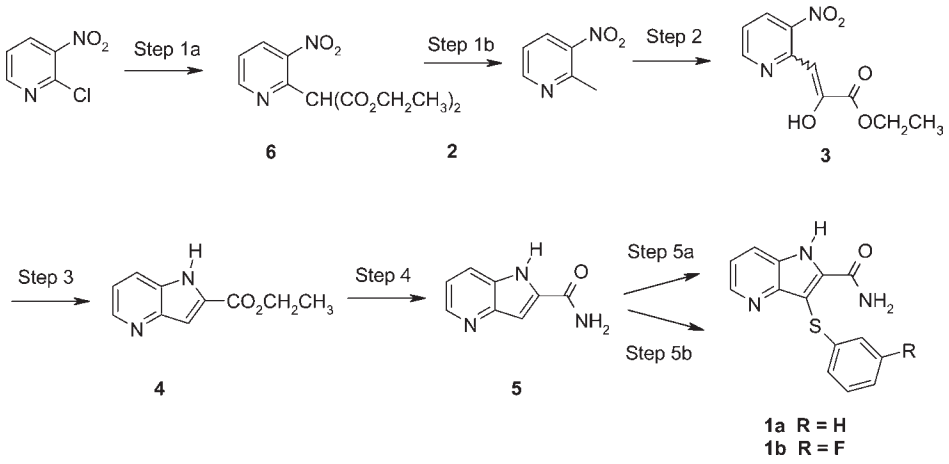
Scheme 8. Scale-up Synthesis of Drug Substance 1a,b[a]



[a] *1st Generation Process Chemistry*: Step 1. (a) diethyl malonate, NaO^{t}Bu, NMP, 50 °C, 2 h; (b) 6 M aq. H_2SO_4, 100 °C, 7 h, 80%; Step 2. diethyl oxalate, NaOEt, THF, rt, 2 h, 88%; Step 3. Pd/C, EtOH, H_2 (50 psi), 40 °C, 4 h, 85%; Step 4. NH_3 in MeOH, 50 °C, 36 h, 90%; Step 5. (a) diphenyl disulfide, Cs_2CO_3, NMP, 120 °C, 24 h, 84%; (b) bis(3-fluorophenyl) disulfide, Cs_2CO_3, NMP, 120 °C, 2 h, 95%. *Scale*: 10−330 g, Overall yield: 45.2%. *2nd Generation Process Chemistry*: Step 1. (a) diethyl malonate, NaO^{t}Bu, NMP, 50 °C, 2 h; (b) 6 M aq. H_2SO_4, 100 °C, 12 h, 90.1%; Step 2. diethyl oxalate, NaOEt, THF, rt, 2 h, 84% after reslurry; Step 3. Pd/C, $HCOONH_4$, CH_3COOH, EtOH, 35 °C, 2 h, 89.2%; Step 4. NH_3 in ethylene glycol, 65 °C, 6 h, 95%; Step 5. bis(3-fluorophenyl) disulfide, Cs_2CO_3, NMP, 120 °C, 2 h, 97.6%. *Scale*: 5−30 kg, Overall yield: 62.6%.

in this reaction included the ethyl and the methyl esters (Scheme 5). Also observed was the corresponding carboxylic acid **11b**, which was washed away in the filtrate.

Alternative conditions were explored to shorten the reaction times. Literature indicated that similar reactions have been run in aqueous ammonium hydroxide solution.[11] Efforts toward this end showed that the starting material was consumed in just 5 h at 60 °C at ∼20 psi. The best isolated yield from the small scale reactions was 64%. A significant amount of **11b** was formed.

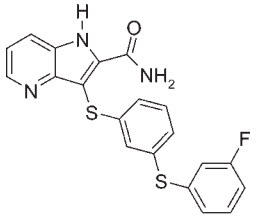
An alternative procedure utilizing ethylene glycol reduced the pressure needed to ∼1 psi and decreased the reaction time to 6 h. Ammonia is reported to have a higher solubility in ethylene glycol than in other solvents such as chlorobenzene, acetone, and butanol.[12] Utilizing this solvent, the amidation was complete at 65 °C in 6 h. This reaction did not generate significant pressure (<1 psi). The yield range was 90−97% with a target purity of greater than 98%. The main impurity was the glycol ester **11c**. It was shown that approximately 2% of glycol ester impurity does not impact the next step in the synthesis.

The plant operators preferred to add the azaindole ester **4** followed by the ethylene glycol. Subsurface addition of gaseous ammonia to the resulting slurry was carried out at room temperature in a closed system, and no heat generation was observed. The reaction was heated to 65 °C for 2 h and then cooled to 20 °C. After adding water, the amide **5** was isolated by filtration. The cake was washed three times with water to remove residual ethylene glycol. The campaign in the plant utilizing the ethylene glycol process provided 17 kg of **5** in four batches in high yield (90−94%) and purity (98.4−98.7%).

Development of Thiophenyl Addition (Step 5). In the original Discovery chemistry route, the amide **5** was treated with the aryl disulfide (1.5 equiv) and cesium carbonate (1.2 equiv) in DMF at 100 °C for 2 days, providing 60% of **1a** (Scheme 6). The low yield was due to an incomplete reaction. Removal of the remaining **5** from the desired product **1a** required flash chromatography.

The reaction was believed to proceed as depicted in Scheme 7. The azaindole amide **5** was deprotonated, and the resulting anion attacked the S−S bond of the aryl disulfide to form the thiophenyl azaindole. The subsequent hydrogen transfer from C3 to N1 was readily achieved with formation of a stable aromatic system. The anion was hydrolyzed to produce product **1a** or **1b**.

It was found that 2.0 equiv of base were essential to drive the reaction to completion. It was also determined that the reaction proceeded faster in NMP than in DMF. The reaction progressed to completion at 120 °C using 2.5 equiv of cesium carbonate and 1.2 equiv of the disulfide. The crude product was precipitated from the reaction mixture by adding water. The excess aryl disulfide was removed by slurrying the crude product in a mixture of ethyl acetate and heptane. The crude drug substance was then recrystallized from MeOH in >85% recovery. In the case of the fluorophenyl disulfide, impurity **12** was observed in the isolated product, suggesting an additional thiophenyl moiety reacting with **1b**.



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The stoichiometry of bis(3-fluorophenyl) disulfide has a strong effect on the formation of **12**. About 0.67% **12** formed when 1.25 equiv of the reagent was used. Use of 1.1 equiv of the reagent worked well, sufficiently driving the reaction to completion while **12** was not detected. The ethylene glycol carried over from step 4 was removed during workup. Under normal conditions, up to 1−2 wt % ethylene glycol was well tolerated.

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Both **1a** and **1b** were prepared on lab scale to support early profiling. Only **1b** was selected as a drug candidate and then prepared at 5 kg scale in the pilot plant.

CONCLUSIONS

This paper describes the development of lab synthesis and a subsequent scale up process for casein kinase I inhibitors (**1a** and **1b**). Introduction of the 2-methyl group was readily achieved via a two-step one-pot process in 90% yield using the cost-effective malonate chemistry. Transfer hydrogenation was implemented in the pilot plant to achieve the desired reductive cyclization. Amidation in ethylene glycol went to completion within a few hours under atmospheric pressure, eliminating the need for a pressure reactor. The overall yield was improved from 17% to 63%. A total of 28 kg of **1b** was prepared and provided for clinical trials. The improved process is summarized in Scheme 8.

EXPERIMENTAL SECTION

General. 2-Chloro-3-nitropyridine was purchased from JVR Fine Chemie Pvt., India, and bis(3-fluorophenyl) disulfide was sourced from Zhejiang Shou & Fu Chemical Co., China. Mass spectra were obtained on a Finnigan MAT TSQ 700 mass spectrometer using electron impact (EI) at 70 eV and chemical ionization (CI) with the relative peak height in percent and the molecular ion designated as M given in parentheses.

HPLC was performed on Luna 5 μ phenyl-hexyl 4.6 mm × 150 mm. Flow rate: 1.0 mL/min; column temperature: 25 °C, equilibrate column for 5 min between runs. Typical total run time: 35 min.

Method for step 1 and 2: Mobile phase: (A) 0.1% TFA in water; (B) 0.1% TFA in acetonitrile. Injection volume: 10 μL, λ = 240 nm; diluting solvent: 50/50 solvent A/solvent B. Gradient from 30% to 40% solvent B over 10 min, then from 40% to 70% over 16 min. Retention times: 2-chloro-3-nitropyridine, 6.5 min; 2-methyl-3-nitropyridine **2**, 4.6 min; aryl malonate **6**, 6.3 min; bis-aryl malonate **7**, 14.8 min; ketoester **3**, 13.1 min; diethyl oxalate: 6.1 min; oxalic acid, 1.5 min.

Method for step 3: Mobile phase: (A) 0.1% TFA in water; (B) 0.1% TFA in acetonitrile. Injection volume: 5 μL, λ = 230 and 290 nm; diluting solvent: methanol. Gradient from 5% to 40% solvent B over 15 min, then from 40% to 95% solvent B over 10 min. Retention times: hydroxyamine **9**, 4.6 min; azaindole ethyl ester **4**, 7.4; *N*-hydroxy azaindole **10**, 8.0 min.

Method for steps 4 and 5: Mobile phase: (A) Dissolve 3.86 g of ammonium acetate in a 1000 mL of HPLC grade water (pH 6.9). Filter the buffer using a 0.45 m nylon filter. (B) Acetonitrile. Injection volume: 5 μL, λ = 230 and 290 nm; diluting solvent: 50/50 water/acetonitrile. Gradient from 5% to 40% solvent B over 15 min, then from 40% to 95% solvent B over 10 min. Retention times: azaindole amide **5**, 6.8 min; glycol ester **11c**, 8.7 min; azaindole ester **4**, 12.9 min; **1b**, 15.6 min; byproduct **12**, 20.8 min; bis(3-fluorophenyl) disulfide, 25.2 min.

2-Methyl-3-nitropyridine (2). A glass lined reactor was charged with sodium *tert*-butoxide (11.7 kg, 121.7 mol) and NMP (36 kg) at 20 ± 3 °C. Diethyl malonate (17.7 kg, 110.5 mol) was charged over 45 min at 20 ± 10 °C. The batch was agitated at 20 ± 3 °C for 15 min. A preprepared solution of 2-chloro-3-nitropyridine (8.75 kg, 55.2 mol) in NMP (23 kg) was charged over 45 min at 20 ± 5 °C (note: higher temperatures must be avoided as it can lead to formation of diaryl byproduct **7**). The reactor was heated to 50 ± 3 °C and held for 2 h. A sample was taken and analyzed by HPLC, and the reaction was considered complete when ≤0.5 A% of 2-chloro-3-nitropyridine remained (actual amount = 0.14 A%). A solution of 6 M sulfuric acid (57 kg) was charged over 25 min at 50−60 °C (note: the sulfuric acid addition is exothermic, and the batch thickens during the first 20% of the charge. As the addition proceeds, a complete solution is obtained with the color change from dark brown to orange). The reaction was heated to 100 ± 3 °C and held for 10 h. A sample was taken and analyzed by HPLC. The reaction was considered complete when ≤1 A% of the monoester **6** remained (actual amount =0.44 A% A% = Area%). The batch was cooled to 15 ± 5 °C and transferred to a glass lined reactor. Toluene (76 kg) was charged to the reactor. A solution of 45 wt % potassium hydroxide (105 kg) was charged over 45 min at 20 ± 10 °C. The batch was filtered through Celite (4.0 kg). The filter cake was washed with water (16.4 kg), and the toluene layer was separated (agitated for 15 min, then settled for 15 min). The aqueous layer was extracted with toluene (76 kg). The combined toluene layers (146.8 kg) were distilled at 100 Torr, and reactor temperature was gradually adjusted up to 90 °C until the batch was at the minimum stirred volume (~20 L). The batch was cooled to 20 ± 10 °C to yield a solution of **2** in toluene (total weight: 11.8 kg, 58.5 wt %, 90.1% yield). An aliquot was distilled to provide a sample for analysis: ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.70 (d, 1H), 8.25 (d, 1H), 7.35−7.40 (m, 1H), 2.85 (s, 3H).

2-Hydroxy-3-(3-nitropyridin-2-yl)acrylic Acid Ethyl Ester (3). A glass lined reactor was charged with sodium ethoxide (8.8 kg, 129.3 mol) and THF (65 kg). The reaction was adjusted to 10 ± 3 °C. Diethyl oxalate (29 kg, 198.4 mol) was charged over 30 min at 10 ± 5 °C. The batch was held at this temperature for 30 min. The toluene solution of **2** (8.5 kg, 48.9 wt % and 8.35 kg, 58.1 wt %, corresponding to 9.0 kg of **2**, 65.2 mol) was charged over 20 min at 10 ± 5 °C. The reactor was warmed to 20 ± 3 °C and held for 2 h. A sample was taken and analyzed by HPLC. The reaction was considered complete when <1.0 A% of **2** remained (actual amount = 0.2 A%). Ammonium chloride solution (87 kg, preprepared from 17.4 kg of ammonium chloride and 69.6 kg of water) was charged over 1 h at 20 ± 5 °C. Water (16 kg) and isopropyl alcohol (32 kg) were added, and the mixture was stirred at 20 ± 5 °C for 1 h. The batch was filtered, and the cake was washed with water (2 × 54 kg). Once the rate of filtrate collection slowed, the cake was transferred to a second glass lined reactor. Water (210 kg) was charged, and the suspension was stirred (100 rpm) at 20 ± 5 °C for 1 h. The batch was filtered, and the cake was washed with water (2 × 27 kg). The filter cake was dried at 130 Torr and 45 ± 5 °C to reach LOD ≤ 2.0 wt % (actual: 0.41 wt % in 2 days) to provide **3** (13.1 kg, 84.1% yield, 96.46 wt %). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 14.60 (br, 1H), 8.70 (d, 1H), 8.40 (m, 1H), 7.35−7.40 (m, 2H), 4.20 (q, 2H, OCH_2CH^3), 1.40 (t, 3H, OCH_2CH_3); ^{13}C NMR: (75 MHz, $CDCl_3$) δ: 163.2, 156.2, 151.5, 150.0, 142.0, 134.7, 121.2, 98.2, 62.4, 14.4.

1*H*-Pyrrolo[3,2-*b*]pyridine-2-carboxylic Acid Ethyl Ester (4). A glass lined reactor was charged with ketoester **3** (8 kg, 33.6 mol) followed by a suspension of 10% Pd/C (1.9 kg) in water (8.8 kg). Ethanol (3C, 66 kg) and glacial acetic acid (10 kg, 5.0 equiv) were added, and the batch was heated to 35 ± 3 °C. A preprepared solution of ammonium formate (0.74 kg) in water (0.96 kg) was charged over 15 min at 35 ± 3 °C (note: an exotherm and off-gas should be observed as an indication of

initiation of the reaction). The second portion of the ammonium formate solution (6.66 kg of ammonium formate in 8.64 kg of water) was charged over 2 h at 35 ± 3 °C. The batch was held for 1 h. A sample was taken and analyzed by HPLC. The reaction was considered complete when <0.1 A% of **3** and <0.5 A% intermediate hydroxylamine remained (actual amount: 0.009 A% **3** and 0.21 A% hydroxylamine). Celite (1.1 kg) was charged, and the batch was agitated for 15 min. The filter was precoated with Celite (1.7 kg). The batch was filtered through Celite, and the filter cake was washed with ethanol (3C, 13 kg) and water (16 kg), sequentially (note: keep the Pd residue water wet as the dry catalyst is highly flammable). The combined filtrate and washes were transferred to a glass lined reactor, and water (96 kg) was charged. The batch was distilled at 60 °C and 150 Torr until the batch was about half volume. The batch was then cooled to 5 ± 5 °C over 1 h, and the pH was adjusted to 8.05 (target range: 8.0 ± 0.5) using aqueous sodium hydroxide solution (2.5 M, 24 kg). The batch was stirred at 5 ± 5 °C for 1 h and filtered. The filter cake was washed with water (2 × 16 kg). The cake was dried at 60 ± 5 °C and 130 Torr to provide azaindole ester **4** (5.7 kg, 89.2% yield, 98.7 wt % pure). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 8.40 (s, 1H), 7.90 (d, 1H), 7.20−7.40 (m, 2H), 4.45 (q, 2H, OCH_2CH^3), 1.40 (t, 3H, OCH_2CH_3); ^{13}C NMR: (75 MHz, $CDCl_3$) δ: 161.6, 144.0, 144.0, 131.1, 120.9, 119.5, 106.5, 61.2, 23.5.

1*H*-Pyrrolo[3,2-*b*]pyridine-2-carboxylic Acid Amide (5). A glass lined reactor was charged with azaindole ester **4** (5.5 kg, 28.9 mol) and ethylene glycol (56.1 kg). The mixture was stirred at 23 ± 3 °C. Ammonia (3.6 kg) was charged through a dip pipe to the closed reactor at 20−35 °C. The mixture was stirred for 15 min at 25 ± 3 °C. The reactor was heated to 65 ± 3 °C over 40 min while venting to the acid scrubber. The batch was held at 65 ± 3 °C for 6 h in the closed reactor. A sample was taken and analyzed by HPLC. The reaction was considered complete when ≥98 A% of **5** was present (actual amount: 98.0 A%). Water (23 kg) was charged, and the batch was cooled to 5 ± 2 °C over 30 min and held at that temperature for 1 h. The mixture was filtered, and the filter cake was washed with water (2 × 33 kg) and dried at 65 °C until water content was <0.5% by Karl Fischer (KF: 0.15% in 24 h) to give **5** (4.45 kg, 95% yield, 97.3 wt %). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 11.60 (br, 1H), 8.40 (s, 1H), 8.20 (br, 1H), 7.80 (d, 1H), 7.60 (br, 1H), 7.15−7.25 (m, 2H); ^{13}C NMR: (75 MHz, DMSO-d_6) δ: 162.5, 145.2, 143.8, 134.3, 129.5, 119.6, 118.8, 102.2.

3-Phenylsulfanyl-1*H*-pyrrolo[3,2-*b*]pyridine-2-carboxylic Acid Amide (1a). A mixture of diphenyl disulfide (177.8 g, 1.5 equiv), Cs_2CO_3 (351.9 g, 2.0 equiv), and amide **5** (87.5 g, 0.54 mol) in NMP (1.20 L) was heated to 120 °C for 21 h. Additional Cs_2CO_3 (87.97 g, 0.5 equiv) was added, and the reaction was held at 120 °C for another 4 h. The reaction was judged to be complete (94% of **1a**, 1.4% of unreacted **5**, 4.5% of PhSSPh). The reaction mixture was cooled to rt and combined with the crude mixture from another batch (starting from 78.1 g of amide **5**) for workup. The combined mixture was poured into ice−water (6 L) and stirred for 1 h. The brown colored solid was filtered-off, washed with water (2 × 300 mL), and air-dried for 6 h. The solids were twice slurried with 20% EtOAc/heptane (2.0 L) at rt to remove PhSSPh. The crude product was divided into two batches (150 and 154.8 g), and each treated with charcoal in THF (6.0 L) at reflux for 1 h. The mixture was cooled to room temperature and filtered through Celite, and the filtrate was concentrated to give light brown solids (122 and 137 g), respectively. The isolated yield was 94%. ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.60 (br, 1H), 8.50 (s, 1H), 8.20 (br, 1H), 7.95 (d, 2H), 7.20 (m, 4H); ^{13}C NMR: (75 MHz, DMSO-d_6) δ: 161.1, 145.3, 144.9, 136.8, 136.4, 129.9, 128.9, 125.9, 125.4, 120.5, 119.5, 101.0.

3-(3-Fluorophenyl)sulfanyl-1*H*-pyrrolo[3,2-*b*]pyridine-2-carboxylic Acid Amide (1b). A glass lined reactor was charged with **5** (5 kg, 31.0 mol), cesium carbonate (26 kg, 79.8 mol, 2.5 equiv), and NMP (52 kg). The mixture was stirred at 25 ± 5 °C. Bis(3-fluorophenyl) disulfide (8.7 kg, 34.2 mol, 1.1 equiv) was charged. The batch was heated to 120 ± 5 °C and held for 1 h. The batch was cooled to 75 ± 5 °C for sampling. The reaction was considered complete when ≤0.5 A% of **5** present (actual amount: 0.14 A%). Water (50 kg) was charged over 45 min at 15−30 °C. The batch was stirred at 20 ± 5 °C for 1 h and then filtered, and the cake was washed with water (2 × 25 kg). The cake (15.6 kg) was transferred into a Hastelloy reactor. Heptane (50 kg) was charged followed by ethyl acetate (17 kg). The mixture was stirred at 20 ± 5 °C for 1 h and filtered. The cake was washed with heptane (2 × 8 kg) and dried at 40 ± 5 °C and 130 Torr to give **1b** (8.7 kg, 97.6% yield). ^{1}H NMR (300 MHz, DMSO-d_6) δ: 12.60 (br, 1H), 8.55 (s, 1H), 8.20 (d, 1H), 7.95 (m, 2H), 7.30 (m, 2H), 6.80−7.00 (m, 3H); ^{13}C NMR: (75 MHz, DMSO-d_6) δ: 161.3, 145.4, 145.3, 137.0, 130.9, 130.8, 129.9, 122.0, 122.0, 120.8, 119.7, 112.8, 112.5, 100.1.

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