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Development of a Practical Synthesis of a p38 Kinase Inhibitor via a Safe and Robust Amination

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ABSTRACT: The development of a practical synthesis for a p38 kinase inhibitor is described. The key advances include an improved route to the key intermediate, a substituted pyrrole, and a subsequent animation utilizing *O*-(4-nitrobenzoyl)-hydroxylamine, which provides a safe, scalable, and robust amination method. The new protocol was successfully demonstrated to generate 1.6 kg of API in seven steps and 26% overall yield.

INTRODUCTION

Pyrrolotriazine **1** was identified as a lead candidate for efficient p38α kinase inhibition and was chosen for development as a potential therapy for rheumatoid arthritis and other inflammatory diseases.[1]

In the initial Discovery Chemistry synthesis of **1** (Scheme 1), condensation of ethyl isocyanoacetate with acetaldehyde under basic conditions afforded pyrrole **2**.[1−3] Subsequent *N*-amination of **2** with *O*-(2,4-dinitrophenyl)hydroxylamine provided aminopyrrole **3**, which reacted with formamide to complete the pyrrolotriazine ring system to produce **4**. Following chlorination of **4** and coupling with aniline **6**, hydrolysis and amidation with ethylamine completed the synthesis of the API (**1**).

The Discovery synthesis was successful in producing the initial quantities of **1** in good yield. However, further development was necessary to reduce the cost of goods, address safety concerns, and overcome challenging scale-up issues prior to multikilogram preparations. While finding an alternative to the toxic and expensive starting material ethyl isocyanoacetate was important, the key for a viable multikilogram-scale process was to identify safer and more practical reaction conditions for the *N*-amination of **2**. We also sought to address the elevated reaction temperature (160 °C) required for condensation of **3** with formamide, as well as the use of neat $POCl_3$ as solvent for chlorination of **4**. In this report, we describe a successful development program that overcame these challenges and provided a practical process for implementation of the route on the multikilogram scale.

RESULTS AND DISCUSSIONS

I. Preparation of Pyrrole 2. The initial synthesis of **2** via condensation of ethyl isocyanoacetate with acetaldehyde afforded the desired product in an acceptable yield (66%). However, the isocyanoacetate was both costly and toxic, and isolation of the product required chromatography. As an alternative, we initially investigated a slightly longer preparation which utilized readily available ethyl acetoacetate and glycine ethyl ester[4,5] as starting materials (Scheme 2). In the described procedure, ethyl acetoacetate was condensed with *N*,*N*-dimethylformamide dimethylacetal in refluxing toluene to generate a dimethyl enamine intermediate **9a**. Isolation of the dimethyl enamine and treatment with glycine ethyl ester HCl and acetic acid at 100 °C afforded **9** in 49% yield from ethyl acetoacetate.[4b] Our development work led to the use of tosic acid as catalyst for the condensation under neat conditions at 55 °C. In addition, the condensation product **9a** was not isolated and the enamine exchange with glycine ethyl ester HCl was conducted in ethanol at 50 °C. This optimized process reproducibly provided a 78−82% yield of enamine **9** from ethyl acetoacetate.

Cyclization of **9** under literature conditions (NaOEt/EtOH)[5] produced **2** in only 40% yield with 90% HPLC area purity. A screen of reaction conditions indicated that the cyclization required polar protic solvents and the presence of strong bases, such as NaOEt potassium *tert*-amylate or $KOBu^t$ at 60 °C. We proposed a mechanism (Scheme 3) in which the initial cyclization to form intermediate **12** was reversible. Protic solvents facilitate protonation of **12** and lead to the irreversible elimination of water to generate pyrrole **2**. Under these conditions, impurities **10**, **14a**, and **14b** were observed at combined levels up to 40 mol %. We hypothesized that the 1 equiv of water generated during the cyclization causes the formation of impurities **10**, **14a**, and **14b** via hydrolysis of **2** and **9**. A variety of water scavenging reagents and additives, such as molecular sieves, anhydrous Na_2SO_4, TFAA, TsCl, Tf_2O, TMSOTf, and ethyl trifluoroacetate, were investigated. Ethyl trifluoroacetate was found to be the most effective additive and minimized the hydrolysis impurities to 10 mol % in the completed reaction mixture. It appears that ethyl trifluoroacetate acts as a sacrificial ester, being more reactive toward water than the ester groups of **9** and **2**. After the addition of 2 equiv of base to sequester any trifluoroacetic acid generated, pyrrole **2**

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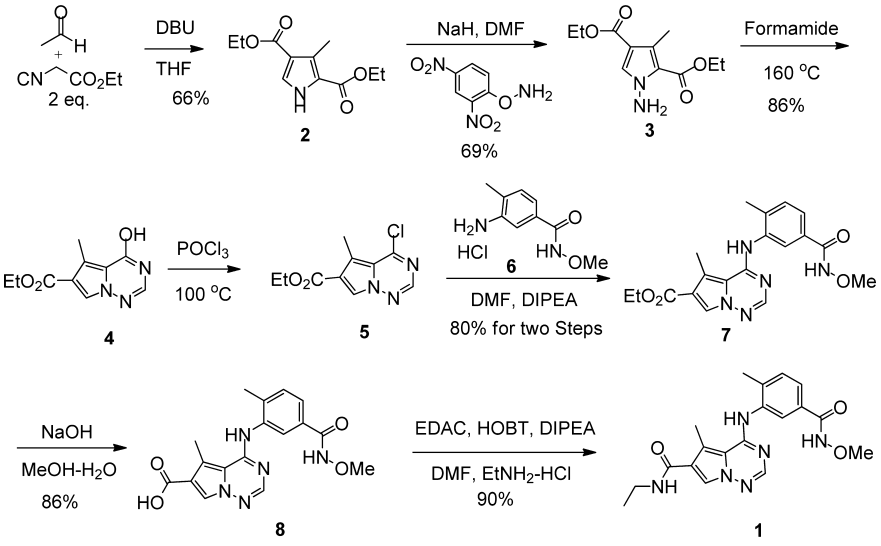
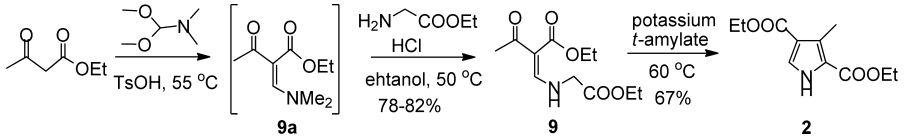
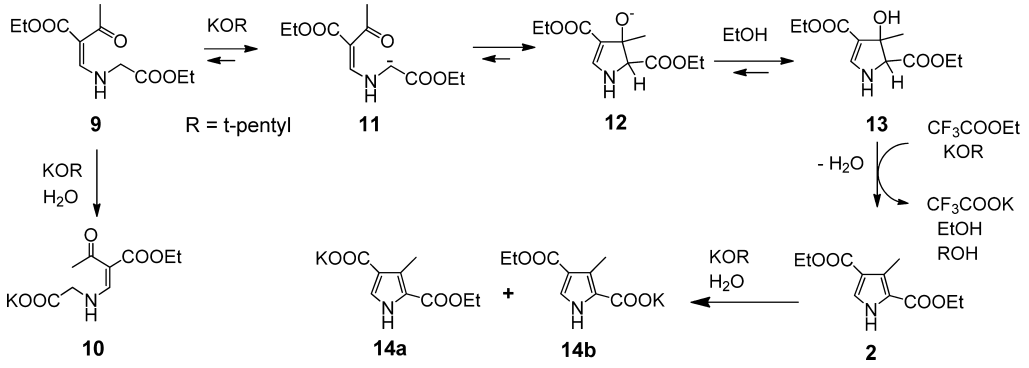
Scheme 1. Discovery Chemistry Synthesis of 1



Scheme 2. Alternative Synthesis of Pyrrole 2



Scheme 3. Proposed Mechanism for Formation of Pyrrole 2



was isolated as a yellow solid in 60−70% yield in good quality (96% HPLC area purity) on up to 12 kg input scale.

II. Amination of Pyrrole 2 to Amino Pyrrole 3. *Chloramine Amination.* The efficient annulation of a triazine ring onto the pyrrole **2** required *N*-amination followed by condensation with formamide (Scheme 1). Although the Discovery Chemistry reaction of **2** with *O*-(2,4-dinitrophenyl)-hydroxylamine provided **3** in good yields, concerns regarding the detonation potential[6] as well as the toxicity of the resulting 2,4-dinitrophenol byproduct required consideration. In addition, the use of NaH in DMF is hazardous.[7] There are not many *N*-amination conditions that lend themselves to the safety, cost, and scalability requirements of a viable multikilogram-scale process. Thus, work focused on identifying alternative reagents to fulfill these requirements.

Chloramine (NH_2Cl) had been found earlier to be an effective reagent for the amination of **2**.[8] For the initial scale-up batches, the amination reaction was carefully optimized to enhance safety, ensure consistent performance, and minimize the competing degradation of the aminopyrrole product **3** under the reaction conditions. The cleanest reaction profile was achieved when treating a solution of pyrrole **2** in DMF or DMAc in presence of 2 equiv of KOBu^t with 1.4−2 equiv of an anhydrous solution of chloramine in MTBE.[9] In the presence of >2 equiv of the base, aminopyrrole **3** reverted to pyrrole **2**. When using a higher excess of chloramine, **3** degraded to form 2-chloropyrrole **3a** (Figure 1). The same degradation product (**3a**) was found when treating **3** with aqueous HCl.[10]

Employing the optimized reaction conditions, 99% HPLC area in-process purity and 86% isolated yield of **3** could be achieved. However, due to the limited miscibility of the DMF

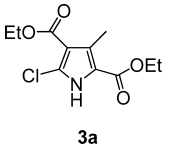


Figure 1. Structure of aminopyrrole degradation product **3a**.

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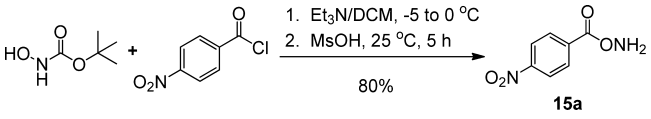
and MTBE phases in the reaction, the reaction was mass transfer controlled and yields declined on scale up due to decreasing surface/volume ratios and less efficient mixing.

In order to overcome the mass transfer issue as well as increase volume efficiency, we subsequently developed a process to aminate **2** using gaseous chloramine, generated from chlorine and ammonia in a continuous fashion.[11] This new process was successfully employed to prepare aminopyrrole **3** in a 74% yield at up to a 2 kg scale. However, due to the complexity of the setup and safety concerns around the use of chlorine gas, we continued to seek more robust amination reagents and conditions.[12]

O-(4-Nitrobenzoyl)hydroxylamine Amination. Amination of heterocycles has been reported using a variety of hydroxylamine-based electrophilic NH_2^+ equivalents, such as *O*-acyl,[13] *O*-alkyl,[14] *O*-sulfonyl,[15] *O*-nitrophenyl,[16] and *O*-diarylphosphinyl[17] derivatives. Unfortunately, most of these reagents are not commercially available, or they are thermally instable. Only hydroxylamine−*O*-sulfonic acid (HOSA) has been used on-scale.[18] However, HOSA was not a suitable reagent, since the electron-deficient pyrrole **2** was too unreactive to provide more than 5−10% conversion in spite of extensive experimentation.

Friestad and co-workers reported the NH_2^+ transfer to the nitrogen of a cyclic carbamate through the use of *O*-(4-nitrobenzoyl)hydroxylamine **15a** (Scheme 4).[13a] This reagent

Scheme 4. Preparation of *O*-(4-Nitrobenzoyl)hydroxylamine 15a

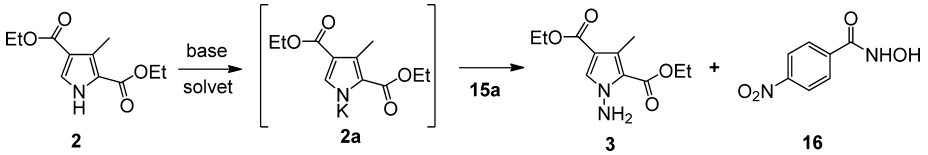


appeared promising, and we were very pleased to observe efficient amination of **2** with **15a**. Since **15a** was not readily available in large quantities, we developed a process based on literature methods[13b,14a] that provided **15a** in a single step from *p*-nitrobenzoyl chloride and *N*-Boc-hydroxylamine in 80% yield and 99% purity. Our studies also indicated *O*-(4-nitrobenzoyl)-hydroxylamine **15a** was stable at room temperature in its crystalline form for up to six months and at 0 °C for more than two years. This provided a reasonable shelf life for storage and use in manufacturing. The thermal stability analysis of **15a** displayed exothermic events with onset temperatures at 100 °C (641 J/g) and 162 °C (657 J/g), which offered a reasonable margin of safety if the amination was executed at 25−35 °C. Based on these results, we concluded that **15a** could be considered for use on multikilogram-scale and demonstrated its applicability to the *N*-amination of a variety of heterocyclic substrates.[19]

An extensive solvent and base screen revealed that the counterion of the base had a profound impact on the amination of pyrrole **2** with the hydroxylamine **15a** (Table 1). Generally, the reactivity increased with less complexing counterions. For example, while lithium bis(trimethylsilyl)amide led to only 6% conversion in THF, sodium bis(trimethylsilyl)amide yielded 21% and potassium bis(trimethylsilyl)amide gave 76% conversion to the desired aminopyrrole **3** (entries 1−3). The same trend was observed in THF 3:7 NMP mixtures (entries 5−7). A major byproduct, particularly in the presence of lithium, was *p*-nitrobenzohydroxamic acid (**16**).[20] We hypothesized that complexation of **15a** by metal cations facilitated isomerization of the hydroxylamine to the hydroxamic acid **16**. The resulting decomposition of the aminating reagent coupled with the protonation of the pyrrole anion **2a** by **16** led to low yields in the presence of strongly complexing cations such as lithium. Higher yields were achieved in the more polar NMP/THF solvent system than in 100% THF in accordance with our hypothesis, as the metal-complexation would be stronger in 100% THF. Moisture also had a significant impact on the reaction. Lower conversion (84% vs 92%) was observed in the presence of more water, which was probably due to competitive reaction of water with the aminating agent.[19] The bases KHMDS and KOBu^t in NMP 7:3 THF provided the best conversion (92%).

During further development of the amination process, we noticed the presence of impurity benzoylamide **17** that persisted at 2−5% HPLC relative area purity (Scheme 5). Crystallization of aminopyrrole **3** was problematic, and thus, **17** had to be carried over into the subsequent formation of

Table 1. Optimization of Amination Reaction[a]



entry	base (1.1 equiv)	solvent syst	react. time	conv[b]	hydroxamic acid **16**
1	LiHMDS	THF	2 h	6%	55%
2	NaHMDS	THF	3 h	21%	42%
3	KHMDS	THF	2 h	76%	9%
4	KOBu^t	THF	2 h	75%	11%
5	LiHMDS	NMP-THF (7:3)	2 h	63%	21%
6	NaHMDS	NMP-THF (7:3)	2 h	79%	10%
7	KHMDS	NMP-THF (7:3)	2 h	92%	4%
8	KOBu^t	NMP-THF (7:3)	2 h	92%	2%
9	KOBu^t	NMP-THF (7:3)	2 h	84%[c]	8%
10	K_2CO_3	NMP	70 h[d]	33%	1%
11	Cs_2CO_3	NMP	20 h[d]	85%	1%

[a]Reactions were run with 1.2 equiv of **15a**. [b]By HPLC analysis. [c]1 equiv of water added. [d]Slow reaction, probably due to solubility issue of base.

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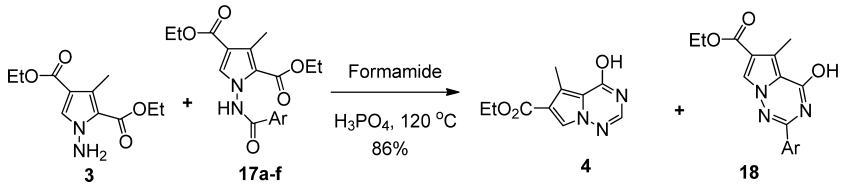
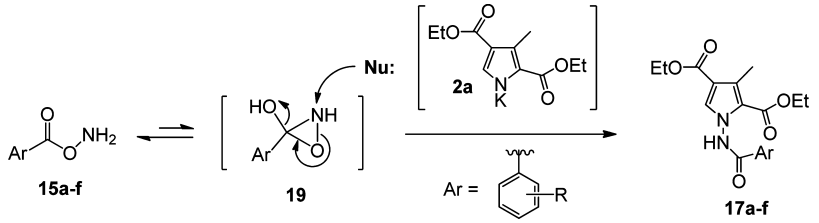
Scheme 5. Conversion of 17 to 18



Scheme 6. Proposed Mechanism of the Formation of Impurity 17



pyrrolotriazine **4**. It was shown that **17** transformed in the subsequent condensation with formamide into arylated pyrrolotriazinone **18**. Due to the structural similarity of **18** with pyrrolotriazine **4**, the arylated pyrrolotriazinone **18** and its resulting impurities could not be efficiently purged from any of the intermediates downstream. This made identification of conditions to minimize the level of impurity **17** critical to the successful production of high quality API.

Control experiments indicated that **17** was not generated by the reaction of aminopyrrole **3** with *O*-(4-nitrobenzoyl)-hydroxylamine **15a**. Significantly, a reverse addition of the pyrrole anion **2a** to reagent **15a** afforded a reduced level of **17** to 1−2%. Monitoring the impurity profile over time also indicated that **17** was generated continuously from the beginning of the amination reaction. Based on these observations, we developed a mechanistic proposal (Scheme 6). We hypothesized that, under strong basic conditions, **15a** formed low levels of 3-hydroxyl-oxaziridine **19**. Nucleophilic attack by the pyrrole anion **2a** and ring-opening of **19** is the source of benzoylamide **17**.

Based on the proposed mechanism, we rationalized that benzoyl hydroxylamine reagents with electron donating substituents should be less prone to generate the corresponding 3-hydroxyl-oxaziridines and accordingly result in less benzoylamide byproducts in the amination reaction. To verify this assumption, we prepared a series of substituted *O*-benzoyl hydroxylamines **15b−f**[19] and determined the levels of the corresponding benzoylamides **17b−f** in the amination reaction (Table 2). In accordance with our hypothesis, we found that the levels of the benzoylamide byproduct decreased with more electron-donating aromatic substituents. *O*-(4-Methoxy)-hydroxylamine (**15f**) proved to be the most effective amination reagent, reducing the level of byproduct **17f** to 0.3 HPLC area percent purity with excellent conversion (97%).

Table 2. Results of Cyclization of Substituted *O*-Benzoyl Hydroxylamines

reagent	R-	substituent const (σ)[21]	conv (%)[a]	byproduct **17a−f** (%)[b]
15a	4-NO_2	0.78	92	4.5
15b	4-F	0.06	93	1.7
15c	3-Cl	0.37	95	1.5
15d	4-Br	0.23	96	1.1
15e	4-Cl	0.23	95	0.6
15f	4-OMe	−0.27	97	0.3

[a]HPLC % conversion after 0.5−3.0 h at room temperature. [b]HPLC area percent.

In parallel with these approaches, we also pursued options to purge impurity **17a** from the reaction stream by selective reactivity. We found that **17a** could be reduced to the related aniline derivative by treating the amination reaction mixture with aqueous sodium dithionate solution. The corresponding aniline derivative stayed in the aqueous layer during extractive workup and was removed from aminopyrrole **3**. After incorporating this protocol into the amination/cyclization sequence, the levels of impurity **18** in **4** could be reduced to <0.05% HPLC area purity.

Having identified two approaches to control the level of benzoylamides **17**, we ultimately chose to pursue the extraction approach for scale-up due to the low melting point (35 °C) of reagent **15f**.

III. Cyclization to Pyrrolotriazine 4. Optimization work in the subsequent condensation of **3** with formamide to form triazinone **4** focused on lowering the reaction temperature (160 °C). Screening a series of acids[22] revealed that acetic acid, formic acid, or phosphoric acid was an effective catalyst, affording complete conversion in 24 h at 120 °C. An added benefit was pyrrolotriazine **4** was now being obtained as a light yellow solid in 91% yield rather than the previously obtained dark solid. Formic acid was not further developed due to concerns about stability at high temperatures.[23] The use of acetic acid produced the methylated impurity **20** at 1−3% (Figure 2).[24] Since impurity **20** was difficult to remove from the desired product **4**, we selected phosphoric acid (0.2 equiv) as catalyst for the cyclization reaction (20 h at 120 °C). The optimized amination−cyclization process was smoothly scaled up to 8 kg scale and produced **4** in 78−82% yield with >98% HPLC area purity.

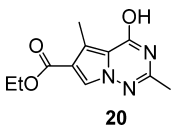


Figure 2. Impurity **20** from acetic acid conditions.

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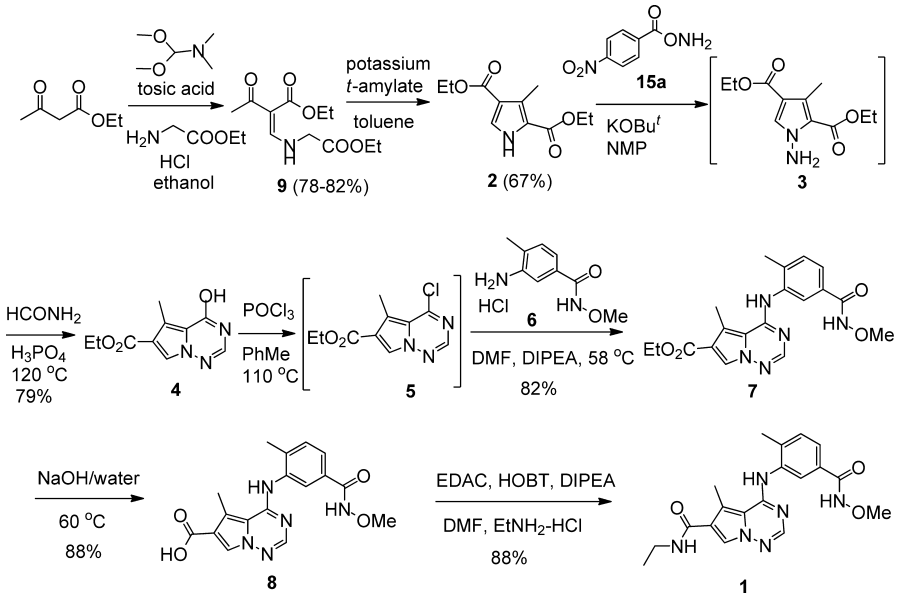
Scheme 7. Multikilogram-Scale Synthesis of 1



IV. Chlorination of Pyrrolotriazine 4 and Coupling with Aniline 6. For the Discovery route, the chlorination of pyrrolotriazine **4** was performed in neat $POCl_3$ at 100 °C. The subsequent highly exothermic quench of the reaction with base led to hydrolysis of ~10% of chloride **5** back to **4**. To address this issue, we screened various reaction conditions and solvents to reduce the amount of $POCl_3$ required. By using toluene as the solvent, $POCl_3$ could be reduced to 3−4 equiv. Addition of 1 equiv of DIPEA further enabled reduction of $POCl_3$ to only 1.2 equiv and decreased the reaction time from >30 h to ~16 h. The optimized reaction conditions also controlled the hydrolysis of chloride **5** to <2%. Due to the limited stability of isolated chloride **5** above −10 °C, we decided to telescope the chlorination into the subsequent amide coupling. This was done by simply performing a solvent exchange from toluene to DMF after the workup.

Hydrolysis of chloride **5** remained a concern during the coupling with aniline **6**. Under the initial reaction conditions, without addition of base, about 15% of **5** would hydrolyze to **4**, which was probably due to the presence of HCl generated in the reaction to accelerate the hydrolysis. Since the process can only tolerate 5% of **4** for isolation of **7**, purging of **4** required several successive crystallizations from DMF−water and ethanol, followed by reslurrying in IPA or MeCN. However, with addition of 1 equiv of DIPEA to the coupling mixture to neutralize the released HCl from reaction, hydrolysis of **5** was reduced to ~3% and the product **7** could be crystallized directly from the reaction mixture by the addition of water.

The preparation of intermediate **7** from **5** was successfully executed by this telescoped process in 88% yield (>98% HPLC area purity) on a 2.2 kg scale.

V. Hydrolysis of 7 to Acid 8 and Subsequent Coupling with Ethylamine. Hydrolysis of **7** was accomplished by treatment with NaOH at 60−65 °C. Upon neutralization, **8** crystallized directly from the reaction mixture. The selection of acid greatly impacted the ease of filtration. Adding 1 N HCl directly to the basic reaction mixture provided **8** as very fine particles that were slow to filter. In contrast, if the reaction mixture was first diluted with one equal volume of water, and then neutralized by slow addition of 1 N acetic acid to a pH 6.0−7.0, **8** was obtained as a fast-filtering granular solid with a density of 2.0 cm^3/g in 88% yield and 98.9% HPLC area purity.

Finally, the resulting acid was converted to the drug substance (**1**) by coupling with ethylamine−HCl using HOBT/EDAC-HCl in DMF.[25] The API (**1**) could be directly crystallized from the reaction mixture by addition of water. The coupling process was scaled to deliver 1.6 kg of **1** in a single batch in 88% isolated yield and >99.0% HPLC area purity.

■ CONCLUSIONS

A practical and safe synthesis of **1** has been developed (Scheme 7). Improvements to the initial process included demonstration of a new, safe, and robust *N*-amination method for pyrrole **2** and optimization of the subsequent reactions for implementation in scale-up facilities. Detailed studies were conducted in order to understand and minimize the formation of impurities in the amination process. In addition, a more cost-effective and less toxic alternative synthesis of pyrrole **2** from ethyl acetoacetate was developed. The optimized processes were executed at multikilogram scale to prepare a total of 1.6 kg of **1** in a 26% overall yield.

■ EXPERIMENTAL SECTION

All reagents purchased from vendors were used as received unless otherwise indicated. Reported yields have not been corrected for impurity levels or moisture content. HPLC method: Waters XTerra RP-18, 3.5 μm, 4.6 mm × 50 mm, 10% water/acetonitrile to 0.2% H_3PO_4/water, 2.5 mL/min, 8 min gradient, 256 nm with retention time of 5.3 min for **2**, 5.1 min for **3**, and 2.2 min for **16**.

Ethyl 2-(((2-Ethoxy-2-oxoethyl)amino)methylene)-3-oxobutanoate (9). A mixture of ethyl acetoacetate (115.5 kg), *N*,*N*-dimethylformamide dimethyl acetal (110.0 kg), and toluenesulfonic acid monohydrate (0.231 kg) was stirred at 55−60 °C for 1 h and then cooled to 45 °C over 1 h. Glycine ethyl ester hydrochloride (123.2 kg) and ethanol (229.3 kg) were added to the above solution, which was then stirred at 45−53 °C for 0.5 h. The reaction mixture was then cooled over 1 h to 20−26 °C and held at 20−26 °C for 2 h. Water (231 kg) was added over 30 min at 20−35 °C (mild exotherm).

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Additional water (1155 kg) was added at 30−35 °C over 2 h to give a thick slurry, which was then cooled to 20 °C over 1 h and held for 2 h. The solid product was collected by filtration. The wet cake was washed with water (1200 kg) and heptane (300 kg) and dried at 35−40 °C under vacuum to give 158.4 kg (78%) of **9** as a slightly yellow solid (known compound in literature). mp 70.0−72.0 °C.[4b] Elemental Analysis: Calcd for $C_{11}H_{17}NO_5$: C, 54.31; H, 7.04; N, 5.76. Found: C, 54.18; H, 7.13; N, 5.58.

Diethyl 3-Methyl-1*H*-pyrrole-2,4-dicarboxylate (2). A solution of potassium *tert*-amylate (1.7 M in toluene, 61.3 L, 53.9 kg, 104 mol) was added over 30 min to a solution of **9** (12.0 kg) and CF_3COOEt (6.8 kg) in toluene (13.0 kg) containing ethanol (25.0 kg) at <27 °C (mild exotherm). The solution was then heated to 60−63 °C over 1 h and stirred at 60−63 °C for 9 h. The reaction mixture was cooled to 15−20 °C over 1 h and quenched with HOAc (4.2 kg) at <25 °C. The resulting mixture was treated with water (64 L). The organic layer was separated and washed with aqueous K_2HPO_4 (6%, 80 kg). The organic solution was filtered through a Zeta Pad (ZP04701-R52SP) which was then rinsed with toluene (10 kg). The filtrate was concentrated to ∼20 L at 35−45° under vacuum. After the reaction mixture was cooled to ∼25 °C over 1 h, heptane (68 kg) was added over 20 min for crystallization. The resulting slurry was stirred at 20 °C for 2 h. The solid product was collected by filtration, washed with heptane (21 kg), and dried under vacuum at 20−30 °C for one day to give 7.5 kg (67%, 95% HPLC area purity) **2** (known compound in the literature) as a yellow solid. mp 89.0−91.0 °C.[4a] Elemental Analysis: Calcd for $C_{11}H_{15}NO_4$: C, 58.66; H, 6.71; N, 6.22. Found: C, 58.43; H, 6.82; N, 6.37.

***O*-4-Nitrobenzoylhydroxylamine (15a).** This is an improved process based on a literature preparation of the phenyl analogue.[13b] Triethylamine (8.0 kg, 402 mol) was added to a solution of *N*-Boc-hydroxyamine (10.0 kg, 75.1 mol) in dichloromethane (104 L) at room temperature. The solution was cooled to −10 °C over 1 h. A solution of 4-nitrobenzoyl chloride (13.9 kg, 75.1 mol) in dichloromethane (44 L) was added over 2 h at −10 to 0 °C (mild exotherm). The mixture was then stirred at −5 to 0 °C for 60 min. Water (75 L) was added to quench the reaction at <15 °C (mild exotherm). After the reaction mixture was stirred for 15 min, the organic layer was separated. The aqueous layer was extracted with dichloromethane (20 L). The combined organic layers were washed with aqueous K_2HPO_4 (4%, 40 L) and then treated with methanesulfonic acid (10.5 kg, 109 mol) at 25 °C for 5 h. The reaction solution was treated with aqueous K_2HPO_4 (20%, 124 kg) at 25 °C for 5−10 min. THF (100 L) was added. The organic layer was separated, washed with water (50 L), and then concentrated under vacuum at <30 °C to a final volume of 40 L. Heptane (60 L) was added over 2 h to the mixture for crystallization. After the reaction mixture was stirred at 20 °C for 3 h, the solid was collected by filtration, washed with THF−heptane (1:2, 2 × 120 L), and dried under vacuum at 25 °C for one day to give product **15a** (11.4 kg, 83%) as a slightly yellow solid. mp 85.0 °C (dec., lit,[13c] 111.5 °C). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.32 (d, 2H, J = 8.4 Hz), 8.21 (d, 2H, J = 8.4 Hz), 6.76 (s, 2H, NH_2). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.5, 150.8, 133.3, 130.6 (2C), 123.7 (2C). Elemental Analysis: Calcd for $C_7H_6N_2O_4$: C, 46.16; H, 3.32; N, 15.38. Found: C, 46.15; H, 3.14; N, 15.34.

Ethyl 4-Hydroxy-5-methylpyrrolo[2,1-*f*][1,2,4]-triazine-6-carboxylate (4). Solid potassium *tert*-butoxide (5.5 kg) was added to a solution of **2** (10 kg) in NMP (60 L), which was stirred at 20−37 °C until all $KOBu^t$ had dissolved (mild exotherm). After the reaction mixture was cooled to 29 °C, a solution of *O*-(4-nitrobenzoyl)-hydroxylamine **15a** (8.1 kg) in dry THF (30 L, KF < 0.1%) was added over 20−30 min at 28−32 °C. The reaction mixture was cooled to 20−25 °C over 90 min. A solution of sodium dithionite (6.7 kg) in water (93.3 L) was added to the reaction mixture at 20−35 °C (mild exotherm), which was then stirred at ca. 30 °C for 30 min. Toluene (50 L) was added to the reaction mixture, which was stirred thoroughly. The organic phase was separated, and the aqueous layer was further extracted with toluene (2 × 50 L). The combined organic phases were washed with a 5% sodium hydrogen carbonate solution (60 L) followed by water (60 L). The organic solution was concentrated by distillation at 40−60 °C under vacuum to 10 L. Formamide (80 L) was added to the residue, which was further concentrated at 60−80 °C under vacuum to remove residual toluene (1−2 L). Phosphoric acid (85%, 0.85 kg) was added to the solution, which was then heated to 120−125 °C for 20 h. The reaction mixture was then cooled to 90 °C over 1 h. Water (100 L) was added over 30 min to give a slurry while cooling to 20−25 °C over 2 h. After stirring for 2 h, the solid product was collected by filtration and washed with water (2 × 40 L), methanol (30 L), and toluene (30.0 L). The wet cake was dried under vacuum at 30−40 °C for two days to give 8.0 kg (79%) of **4** (known compound in the literature). mp 215 °C (dec.).[1] ^{1}H NMR (DMSO-d_6, 400 MHz) 11.65 (br s, 1 H), 7.87 (s, 1 H), 7.85 (s, 1 H), 4.24 (q, 2 H, J = 7.0 Hz), 2.61 (s, 3 H), 1.30 (t, 3 H, J = 7.0 Hz). ^{13}C NMR (DMSO-d_6, 100 MHz) 163.4, 155.1, 140.0, 123.2, 122.9, 117.7, 114.0, 59.6, 14.2, 11.0.

Ethyl 4-((5-(Methoxycarbamoyl)-2-methylphenyl)-amino)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylate (7). In the following order, pyrrolotriazine **4** (1.54 kg), toluene (24.4 kg), phosphorous oxychloride ($POCl_3$, 1.3 kg), and *N*,*N*-diisopropylethylamine (1.1 kg) were charged to a reactor and the reaction mixture was stirred at 110 °C for 22 h. The resulting mixture was cooled to 2 °C over 3 h and quenched with cold 18% potassium dibasic phosphate solution (29.4 kg). The quenched biphasic mixture was allowed to settle at room temperature for 1 h. The organic layer was separated and washed with 11% aqueous potassium dibasic phosphate solution (8.0 kg). The organic layer was polish filtered through a 10 μm cuno filter. DMF (8.1 kg) was added to the solution, which was then concentrated under vacuum at 49−53 °C to 9 L and then cooled to 25 °C. A solution of **6** (1.56 kg) in DMF (2.8 kg) containing *N*,*N*-diisopropylethylamine (0.9 kg) was added to the above solution. The mixture was heated to 58 °C. After 25 min, two additional portions of *N*,*N*-diisopropylethyl-amine (0.3 kg each) were added at 30 min intervals. After stirring for an additional 2 h, the reaction mixture was cooled to 20 °C over 2 h. A 9% aqueous potassium dibasic phosphate solution (14.7 kg) was added to give a slurry which was stirred for 20 h. The product was collected by filtration and wash with water (10.5 kg), acetonitrile (3.3 kg), and toluene (6.1 kg). The wet product was dried under vacuum at 30 °C for two days to give 2.2 kg (82%, 98.5% HPLC area purity) dry product (known compound in the literature[1]) as a slightly yellow solid. Elemental Analysis: Calcd for $C_{19}H_{21}N_5O_4$: C, 59.52; H, 5.52; N, 18.27. Found: C, 59.18; H, 5.38; N, 18.23.

4-((5-(Methoxycarbamoyl)-2-methylphenyl)amino)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxylic acid 8. A mixture of ester **7** (2.06 kg), water (6.0 kg), and 50% NaOH

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(1.15 kg) was heated to 60−65 °C over 1 h and then held at 60−65 °C for 5 h. Additional water (7.2 kg) was added at 60−65 °C. A 6 wt % aqueous solution (6.6 kg) of acetic acid was added over 2 h to the solution, which was then held for 40 min. Additional HOAc solution (4.9 kg) was added over 2 h. The resulting slurry was cooled to 25 °C over 2 h and then filtered. The wet cake was washed with water (10 kg) and then heptane (8.0 kg). The wet cake was dried at 70−75 °C under vacuum for two days to give 1.68 kg (88%) of **8** (known compound in the literature[1]) as an off white solid. Elemental Analysis: Calcd for $C_{17}H_{17}N_5O_4$: C, 57.46; H, 4.82; N, 19.71. Found: C, 57.29; H, 4.76; N, 19.53.

***N*-Ethyl 4-((5-(Methoxycarbamoyl)-2-methylphenyl)-amino)-5-methylpyrrolo[2,1-*f*][1,2,4]triazine-6-carboxamide (1).** A mixture of acid **8** (1.66 kg), EDAC (1.076 kg), and HOBt[25] (0.76 kg, CAUTION: HOBt is potentially explosive. Please see references for details) in DMF (7.15 kg) was stirred at 20−25 °C for 3 h. Aqueous 70 wt % ethylamine (0.603 kg) was added to the mixture over 1.5 h at <35 °C. The reaction mixture was stirred at 30−35 °C for 1 h. Water (7.0 kg) was added over 3.5 h to the mixture to give a slurry, which was then cooled to 25 °C over 30 min. After 2 h, the product was filtered, washed with water (8.0 kg) and acetone (6.4 kg), respectively, and dried under vacuum at 25 °C for 2.5 days to afford 1.57 kg (88%) of **1** (known compound in the literature[1]) as an off white solid. Calcd for $C_{17}H_{22}N_6O_3$: C, 59.67; H, 5.80; N, 21.98. Found: C, 59.33; H, 5.64; N, 21.67.

General Method for Preparation of Diethyl 1-(3-Chlorobenzamido)-3-methyl-1H-pyrrole-2,4-dicarboxylate 17a−f from 3. A solution of *m*-chlorobenzoyl chloride (0.48 g, 2.74 mmol) in toluene (5 mL) was added to a solution of **3** (0.76 g, 80 wt %, 2.53 mmol) in toluene (15 mL) at 20−25 °C. After 15 min, a solution of *N*,*N*-diisopropylethylamine (0.48 mL, 0.35 g, 2.7 mmol) in toluene (5 mL) was added over 10 min to the mixture at 17−25 °C. The reaction mixture was stirred at 20−25 °C for 30 min. The reaction was quenched with water (15 mL). The organic layer was separated, washed with 5% aqueous sodium bicarbonate (15 mL) and then water (15 mL), and dried over anhydrous Na_2SO_4 (5 g). The solids were removed by filtration and washed with toluene (10 mL). Concentration of the filtrate under vacuum gave the crude product. This residue was dissolved in MTBE (20 mL), and heptane (15 mL) was added. After the reaction mixture was stirred at 20 °C for 2 h, the resulting crystals were collected by filtration, washed with 1:1 heptane/MTBE (5 mL), and dried under high vacuum at 35 °C for 15 h to give **17c** (R = 3-Cl) as a slightly yellow solid (0.85 g, 79%). mp 120−121 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 10.18 (s, 1 H), 7.91 (t, 1 H, J = 1.7 Hz), 7.77 (ddd, 1 H, J = 7.9, 1.7, 1.5 Hz), 7.73 (s, 1 H), 7.56 (ddd, 1 H, J = 7.9, 1.7, 1.5 Hz), 7.43 (t, 1 H, J = 7.9 Hz), 4.29 (q, 2 H, J = 7.0 Hz), 4.27 (q, 2 H, J = 7.0 Hz), 2.60 (s, 3 H), 1.34 (t, 3 H, J = 7.0 Hz), 1.33 (t, 3 H, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 165.7, 163.9, 162.1, 135.2, 133.1, 132.9, 132.2, 130.6, 130.2, 127.9, 125.5, 118.9, 113.2, 60.8, 59.9, 14.3, 14.2, 11.8. HR-MS: Calcd for $C_{18}H_{19}ClN_2O_5$ + H: 379.1061. Found 379.1062. IR (KBr, cm^{-1}) 3310, 2984, 1721, 1682, 1525, 1419, 1264, 1233, 1079, 775.

Diethyl 1-(4-Nitrobenzamido)-3-methyl-1H-pyrrole-2,4-dicarboxylate (17a). (R = 4-NO_2): 82%. mp 129−130 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) 10.47 (s, 1 H), 8.35 (d, 2 H, J = 8.8 Hz), 8.11 (d, 2 H, J = 8.8 Hz), 7.79 (s, 1 H), 4.30 (q, 2 H, J = 7.2 Hz), 4.28 (q, 2 H, J = 7.2 Hz), 2.60 (s, 3 H), 1.35 (t, 3 H, J = 7.2 Hz), 1.34 (t, 3 H, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) 164.9, 163.9, 162.2, 150.3, 136.8, 131.9, 130.6, 128.8 (2 C), 124.1 (2 C), 118.7, 113.3, 60.9, 60.0, 14.3, 14.2, 11.8. HR-MS: Calcd for $C_{18}H_{19}N_3O_7$ + NH_4: 407.1567. Found 407.1560. IR (KBr, cm^{-1}) 3308, 2991, 1719, 1682, 1529, 1420, 1349, 1268, 1240, 1081, 852, 774.

Diethyl 1-(4-Fluorobenzamido)-3-methyl-1H-pyrrole-2,4-dicarboxylate (17b). (R = 4-F): 74%. mp 119−120 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) 10.17 (s, 1 H), 7.95 (dd, 2 H, J = 8.7, 5.3 Hz), 7.75 (s, 1 H), 7.18 (dd, 2 H, J = 8.7, 8.5 Hz), 4.28 (q, 2 H, J = 7.0 Hz), 4.27 (q, 2 H, J = 7.0 Hz), 2.61 (s, 3 H), 1.33 (t, 3 H, J = 7.0 Hz), 1.32 (t, 3 H, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) 166.0, 165.6 (d, 1 C, J = 255 Hz), 164.0, 162.3, 132.2, 130.7, 130.1 (d, 2 C, J = 10 Hz), 127.5, 118.9, 116.2 (d, 2 C, J = 22 Hz), 113.1, 60.8, 59.9, 14.4, 14.2, 11.9. HR-MS: Calcd for $C_{18}H_{19}FN_2O_5$ + H: 363.1356. Found 363.1359. IR (KBr, cm^{-1}) 3329, 2985, 1716, 1686, 1605, 1504, 1421, 1271, 1230, 1078, 847, 775.

Diethyl 1-(4-Chlorobenzamido)-3-methyl-1H-pyrrole-2,4-dicarboxylate (17e). (R = 4-Cl): 68%. mp 133−134 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) 10.22 (s, 1 H), 7.86 (d, 2 H, J = 8.6 Hz), 7.75 (s, 1 H), 7.47 (d, 2 H, J = 8.6 Hz), 4.28 (q, 2 H, J = 7.2 Hz), 4.27 (q, 2 H, J = 7.2 Hz), 2.61 (s, 3 H), 1.34 (t, 3 H, J = 7.2 Hz), 1.33 (t, 3 H, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) 166.0, 163.9, 162.2, 139.3, 132.2, 130.7, 129.7, 129.9 (2 C), 128.9 (2 C), 118.8, 113.1, 60.8, 59.9, 14.4, 14.2, 11.8. Elemental Analysis: Calcd for $C_{18}H_{19}ClN_2O_5$: C, 57.07; H, 5.05; N, 7.39; Cl, 9.35. Found: C, 57.19; H, 4.88; N, 7.34; Cl, 9.21. IR (KBr, cm^{-1}) 3307, 2983, 1717, 1689, 1677, 1555, 1418, 1264, 1236, 1078, 775.

Diethyl 1-(4-Bromobenzamido)-3-methyl-1H-pyrrole-2,4-dicarboxylate (17d). (R = 4-Br): 50%. mp 141−142 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) 10.22 (s, 1 H), 7.79 (d, 2 H, J = 8.6 Hz), 7.76 (s, 1 H), 7.64 (d, 2 H, J = 8.6 Hz), 4.29 (q, 2 H, J = 7.2 Hz), 4.28 (q, 2 H, J = 7.2 Hz), 2.61 (s, 3 H), 1.34 (t, 3 H, J = 7.2 Hz), 1.33 (t, 3 H, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) 166.1, 164.0, 162.3, 132.3 (2 C), 131.9, 130.7, 130.2, 129.1 (2 C), 127.9, 118.8, 113.1, 60.9, 59.9, 14.4, 14.2, 11.9. HR-MS: Calcd for $C_{18}H_{19}BrN_2O_5$ + H: 423.0556. Found 423.0542. IR (KBr, cm^{-1}) 3299, 2982, 1716, 1689, 1592, 1555, 1529, 1418, 1264, 1235, 1078, 1011, 775.

Diethyl 1-(4-Methoxybenzamido)-3-methyl-1H-pyrrole-2,4-dicarboxylate (17f). (R = 4-OMe): 57%. mp 112−113 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) 10.08 (s, 1 H), 7.89 (d, 2 H, J = 8.8 Hz), 7.73 (s, 1 H), 6.97 (d, 2 H, J = 8.8 Hz), 4.27 (q, 4 H, J = 7.0 Hz), 3.87 (s, 3 H), 2.61 (s, 3 H), 1.33 (t, 3 H, J = 7.0 Hz), 1.31 (t, 3 H, J = 7.0 Hz). ^{13}C NMR ($CDCl_3$, 100 MHz) 166.6, 164.0, 163.3, 162.1, 132.5, 130.6, 129.5 (2 C), 123.4, 119.0, 114.2 (2 C), 112.8, 60.7, 59.8, 55.5, 14.4, 14.2, 11.8. HR-MS: Calcd for $C_{19}H_{22}N_2O_6$ + H: 375.1556. Found 375.1560. IR (KBr, cm^{-1}) 3361, 2985, 1721, 1686, 1674, 1609, 1506, 1419, 1263, 1231, 1174, 1077, 843, 774.

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Notes

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