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Preparation of the HIV Attachment Inhibitor BMS-663068. Part 6. Friedel–Crafts Acylation/Hydrolysis and Amidation

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ABSTRACT: The development of a process for appending the oxalyl amide side chain to the azaindole core of the HIV-attachment inhibitor BMS-663068 is described. A Friedel–Crafts acylation installed the oxalyl ester, which was subsequently hydrolyzed and amidated with a benzoyl piperazine. The development of the commercial route necessitated several key changes to the initial synthesis. For instance, in the original acylation process, nitromethane, a commonly used, but highly energetic cosolvent, was employed which was eventually replaced by catalytic tetra-*n*-butylammonium bisulfate to overcome gelling issues encountered during the reaction when nitromethane was omitted. It was further demonstrated that the amidation sequence could be relegated to a single-pot, homogeneous transformation through the use of the cost-effective coupling reagent diphenylphosphinic chloride. The above modifications have been utilized in multiple campaigns and reproducibly demonstrated on scales of up to 200 kg input.

INTRODUCTION

As was described in our previously disclosed overall synthetic strategy manuscript,[1] following a C7-bromination[2] of the heterocyclic *N*-oxide, the attachment of the oxalyl amide side chain to the 6-azaindole core was the next task required en route to the target API (Scheme 1). This strategy required a Friedel–Crafts acylation, a hydrolysis of the resulting methyl oxalyl ester, and an amidation. Our initial procedures[1] for these chemical transformations were based on literature precedents[3] and involved the use of nitromethane as a cosolvent in the Friedel–Crafts step and carbonyl diimidazole (CDI) to activate the resulting oxalylic acid for the amidation (Scheme 1). While these procedures rapidly provided us with sufficient quantities of amide **3** to support the downstream chemical development, there were several drawbacks from the perspective of scaling up this chemistry. For example, the cosolvent nitromethane is highly energetic,[4] which led to safety concerns as the scale of this transformation increased. Also, the CDI-mediated amidation led to variable product purity. This was due to the fact that the amidation is a two-stage process; that is, the activation of the oxalylic acid and the reaction of the activated acyl imidazole with the amine to yield the desired product. If the amine is introduced prior to the acid being fully activated, numerous impurities can result. Herein, we describe our development efforts which resulted in the strategic evolution of our original procedures to yield a robust manufacturing process.

RESULTS AND DISCUSSION

Friedel–Crafts Acylation and Hydrolysis. Nitromethane is a common cosolvent used in Friedel–Crafts reactions. The polar nature of this solvent facilitates the dissolution of the catalyst, usually $AlCl_3$, and increases the ability of the catalyst to complex with the reaction constituents.[5] These beneficial effects typically lead to homogeneous reaction mixtures and therefore improved reaction rates, which usually result in better reaction yields. There are many examples[6] of Friedel–Crafts reactions performed in the absence of nitromethane. Unfortunately the $AlCl_3$-catalyzed acylation of azaindole **1** with methylchlorooxalate in a solvent system devoid of nitromethane resulted in a difficult-to-agitate reaction mixture due to the formation of a thick gel.[7] Thus, the literature procedures that did not utilize nitromethane as a cosolvent were not viable on scale, forcing us to explore alternate nitromethane-free reaction conditions for this acylation.

Because the thick gels observed during the nitromethane-free reactions were primarily $AlCl_3$-related, we initially investigated reaction conditions that circumvented the use of $AlCl_3$ (Scheme 2). It was hoped that this modification would remove the requirement for nitromethane. The use of indole N1-anions, prepared by deprotonation with Grignard reagents, was among the alternatives initially examined as these substrates were postulated to be more nucleophilic than the neutral indole **1**. Examples have been reported that utilized these anionic substrates where facile acylation was observed without addition of any catalyst.[8] However, acylation of substrate **1** under the same conditions reported in the literature provided less than 5% conversion (Table 1, entry 1). A process for the acylation of an indole derivative using Et_2AlCl has been demonstrated on 3 kg scale,[9] but these conditions were also not applicable to 6-azaindole **1** (Table 1, entry 2), providing only an approximately 19% conversion to acylated product **5**. Other reported procedures that utilized a combination of Grignard reagent

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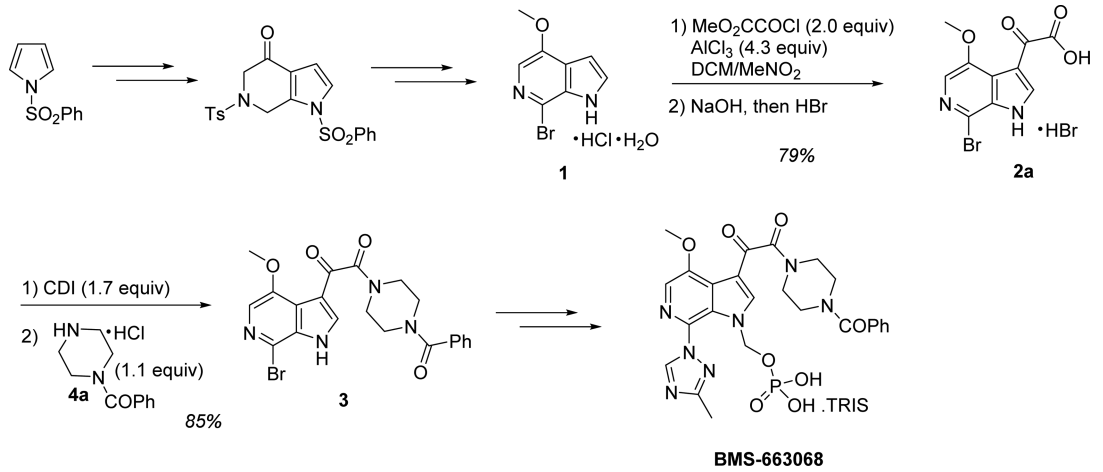
Scheme 1. Original Synthesis of Acid 2a and Amide 3 in the Preparation of BMS-663068



Scheme 2. Acylation of Azaindole 1 to Ester 5

and $ZnCl_2$,[10] 1,5-diazabicyclo[4.3.0]non-5-ene (DBN),[11] various Lewis acids,[12] or a strong Brønsted acid,[13] also performed poorly with our substrate (Table 1, entries 3–8). It has been reported that numerous electron-rich indole substrates can be acylated in the absence of pretreatments or catalysts;[14] however, our substrate was again completely inert when subjected to these conditions (Table 1, entry 9).[15]

As the results in Table 1 illustrate, our attempts to replace $AlCl_3$ catalyst were unsuccessful. Our next approach was to investigate alternative solvents or cosolvents and additives, with the hope of identifying a suitable replacement for nitromethane. However, as shown in Table 2, the use of common dipolar solvents or additives led to extensive gums or gels during the reaction and resulted in low to no conversion of azaindole **1**. Again the low conversions were attributed to poor solubility of the acylation catalyst because all of the reaction mixtures again displayed a thick gel like consistency. Although homogeneous reaction mixtures could be achieved with higher loadings of the additives (>1 g/g input), no acylation took place, presumably due to deactivation of the $AlCl_3$ catalyst by the polar components.

Table 2. Screen of the Acylation Reactions with Polar Additives

entry[a]	additive	quantity (wt %)[b]	conversion[c] (%)
1	methyl sulfone	0.5	7
2	sulfolane	0.5	5
3	DMSO	0.3	0
4	DMF	0.5	0
5	triethyl phosphate	0.3	0
6	trimethylphosphine oxide	0.3	0

[a]Reactions were carried out on a 0.1 g input scale with 2.0 equiv of MeO_2CCOCl, 4.3 equiv of $AlCl_3$ (same amount as that in the previous nitromethane procedure[1a]) in 1.5 mL of DCM for 8–16 h at 21 °C. [b]Weight ratio (g/g) of the additives vs the substrate. [c]The conversion was determined by HPLC analysis as the percentage of the consumed substrate.

Subsequently, we extended our reaction parameter screen to various tetraalkylammonium salts.[16] It was reasoned that the presence of the ionic ammonium salts in the reaction media would increase the polarity of the solvent and potentially resolve the gelling issue due to increased solubility of the catalyst. Conversely, we hoped that the tetraalkylammonium salts would not deactivate the catalyst as had been observed in the previous screens. To our delight, several ammonium salts provided good reaction conversion and produced reaction

Table 1. Screen of $AlCl_3$-Free Acylation Reaction Conditions for Conversion of 1 to 5

entry	conditions	conversion[a] (%)
1	3.1 equiv of EtMgBr, DCM, −20 to 21 °C	<5[b]
2	3.2 equiv of Et_2AlCl, toluene, 0–21 °C	19[b]
3	3.2 equiv of EtMgBr, 1.2 equiv $ZnCl_2$, DCM, 0–21 °C	6[b]
4	0.5 equiv of DBN, toluene, 60–110 °C	0[c]
5	2.0 equiv of $AlBr_3$, DCM, 0–21 °C	70[c,d]
6	2 equiv of $ZrCl_4$, DCM, 21 °C	3[c]
7	1.0 equiv of $FeCl_3$, DCM, 21 °C	4[c]
8	3 equiv of TfOH, DCM, 21 °C	0[e]
9	THF, 0–60 °C	0[b]

[a]Reactions were carried out for 8–16 h on a 0.1 g input scale. The conversion was determined by HPLC analysis as the percentage of consumption of the substrate. [b]1.1 equiv of MeO_2CCOCl were used. [c]2.0 equiv of MeO_2CCOCl were used. [d]Demethylated 4-hydroxyazaindole (18 AP) was observed. [e]1.5 equiv of methyl potassium oxalate were used.

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mixtures that were visually thin slurries that were readily agitated. Representative results are shown in Table 3.

Table 3. Acylation Reactions in the Presence of Ammonium or Lithium Salts

entry[a]	additive	equiv	reaction mixture	conversion[b] (%)
1	Me_4NCl	1.0	gum/gel	15
2	Et_4NCl	1.0	gum/gel	35
3	Pr_4NCl	0.5	gum/gel	22
4	Bu_4NCl	0.5	slurry	87
5	Et_3BnNCl	0.5	gum/gel	38
6	Bu_4NTs	0.5	gum/gel	6
7	Bu_4NPF_6	1.0	slurry	91
8	Bu_4NOTf	0.5	slurry	99
9	Bu_4NHSO_4	0.5	slurry	93
10	LiOTf	0.5	slurry	99

[a]Reactions were carried out on a 0.1 g input scale with 2.0 equiv of MeO_2CCOCl, 4.3 equiv of $AlCl_3$ in 1.5 mL of DCM for 8 h at 21 °C. [b]The conversion was determined by HPLC analysis as the percentage of the consumed substrate.

As shown in Table 3, the studies utilizing ammonium salts revealed that tetra-*n*-butylammonium salts offered the best results when compared to other alkyl analogues (Table 3, entries 1−5) in terms of the conversion and the quality (slurry vs gel) of the reaction mixture. It was also discovered that the counteranion of the ammonium salt played a crucial role. Further screening of tetra-*n*-butylammonium salts identified the superior influence of both the triflate and the bisulfate (Table 3, entries 8 and 9) counteranions. Other common tetra-*n*-butylammonium salts, not listed in Table 3 (e.g., BF_4^-, Br^-, or OAc^-), led to reaction mixtures that contained sticky solids, and as a result, low conversions. Interestingly, lithium triflate was also found to be a suitable additive (Table 3, entry 10), and in the presence of 0.5 equiv, the acylation reaction produced similar results to what was observed in the reactions with the tetra-*n*-butylammonium triflate or bisulfate additives. Other metal salts screened, such as NaOTf, KOTf, or LiCl, failed to enhance the reaction performance, and again the sticky reaction mixtures were observed. Ultimately, *n*-Bu_4NHSO_4 was selected for further optimization due to its significantly lower cost compared to the other options.

Having identified a viable substitute for nitromethane, we next focused our attention on the optimization of the acylation reaction conditions. Typically, two main side products were observed in the reaction mixture, acid **2b** and phenol **6** (Figure 1) derived from the hydrolysis of the ester moiety and demethylation of the C4-methoxy group of compound **5**, respectively. One of the goals for reaction optimization was to minimize the formation of the two side products since they directly impacted both the isolation process and the yield. Table 4 summarizes the key results from the process optimization.

The results in Table 4 suggested that the equivalents and respective ratio of reagents utilized in the reaction have a major impact on the outcome of the acylation, with the stoichiometry of $AlCl_3$ being the most crucial. While 4.0 equiv of the catalyst led to incomplete conversion, a slight increase to 4.5 equiv (compare entries 1−2) led to reaction completion in 5 h. Although increasing the equivalents of $AlCl_3$ further to 5.5 resulted in reaction completion in 3 h, higher levels of side products **2b** and **6** were generated (entry 3). With respect to

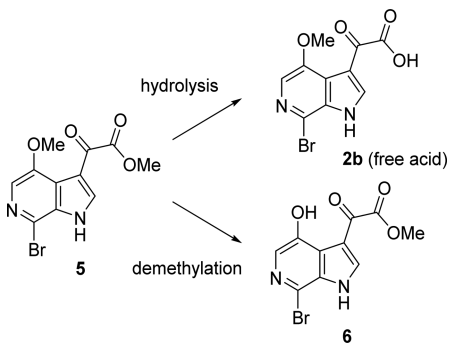

Figure 1. Structures of desired acylated product **5** and side products **2b** and **6**.

methyl chlorooxalate stoichiometry, it was found that 2.1 equiv appeared to be the minimum necessary to achieve >98% conversion (compare entries 4 and 5).

Once we had identified that the inclusion of *n*-Bu_4NHSO_4 was essential for replacing nitromethane and avoiding the formation of gels, we investigated the stoichiometric impact of this additive on the reaction profile. Acylations performed with 0.3−0.8 equiv of *n*-Bu_4NHSO_4 produced stirrable slurries while gumming or gelling was observed when less than 0.3 equiv of *n*-Bu_4NHSO_4 was used (Table 4, compare entries 6−9). In general, higher loadings of the *n*-Bu_4NHSO_4 led to better quality reaction slurries and minimized caking of solids on the reactor wall. However, higher equivalents of the *n*-Bu_4NHSO_4 reduced the reaction rates slightly, although this was the only adverse effect. If desired, a slight increase in the amount of $AlCl_3$ could be utilized to increase the reaction rate with concomitantly higher *n*-Bu_4NHSO_4 loadings. To control production costs and to facilitate subsequent aqueous workup, additional development focused on reactions with lower quantities of $AlCl_3$.

Further optimization led to the identification of the following reproducible and high yielding reaction conditions: 4.6 equiv of $AlCl_3$, 2.3 equiv of methyl chlorooxalate and 0.35 equiv of *n*-Bu_4NHSO_4 in 6 mL/g dichloromethane (DCM). In terms of temperature impact, performing the acylation at ambient temperature led to increased levels of the side product **6** (8 vs 0 AP at 0 °C). Therefore, a reaction temperature of 0 °C was employed for this acylation reaction. The acylations performed under these conditions were typically complete in 8−12 h and afforded the desired product as a mixture of **5** and **2b** in >90% in-process yield. It is worth noting that the reaction mixture initially appeared as a homogeneous solution and then became a slurry during the first 0.5 h of the reaction. HPLC analysis of the reaction slurry supernatant and solids at early conversions (<1 h) revealed that substrate **1** was the primary constituent of the supernatant and that the observed solids were predominately the desired product **5** with <3 AP of the starting azaindole **1** detected. These results indicate that it is unlikely that the reaction proceeds via a slurry to slurry conversion. Presumably after initial dissolution of the substrate, the acylation reaction occurs, and product **5** precipitates from the reaction mixture as a complex with $AlCl_3$. Given that slurry to slurry conversions can result in challenges upon scale-up, these observed reaction attributes were expected to minimize any scale dependent issues. In this context, the reaction kinetics were found to be independent of scale and remained unchanged for reactions ranging from inputs of 0.1−20 g in

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Table 4. Quality and Composition of the Reaction Mixture with Various Equivalents of Reagents

	reagent, equiv				HPLC AP			
entry[a]	$AlCl_3$	$ClCOCO_2Me$	Bu_4NHSO_4	reaction mixture	1	5	2b	6
1	4.0	2.5	0.4	slurry	8	81	2	0
2	4.5	2.5	0.4	slurry	0	90	4	0
3[b]	5.5	2.5	0.4	slurry	0	82	6	3
4	4.5	1.8	0.4	slurry	16	71	5	0
5	4.5	2.1	0.4	slurry	2	89	4	0
6	4.5	2.5	0.2	gum/gel	0	91	3	0
7	4.5	2.5	0.3	slightly sticky slurry	0	88	3	0
8	4.5	2.5	0.8	slurry	6	82	2	0
9	4.8	2.3	0.8	slurry	0	90	5	0

[a]Reactions were carried out on a 0.2 g input scale in 2.0 mL of DCM for 5−8 h at 0 °C. [b]Reaction completed in 3 h.

lab experiments, providing further support for the potential viability to scale this reaction.

With the optimized reaction conditions in hand, our next task was to develop a robust workup and isolation procedure. It was quickly determined that isolating ester **5** would be a challenge since no crystalline forms of ester **5** were found in a screen. Because the hydrolysis of the crude ester **5** produced from the improved acylation reaction stream was very clean,[17] it was determined that the most efficient approach would be to perform an in situ hydrolysis of the ester and then isolate the resulting acid **2b**.

Prior to the hydrolysis of ester **5**, an aqueous workup was required to remove the inorganic salts present in the acylation mixture. Unfortunately, simply following the workup procedure that had been developed for the earlier nitromethane-based process[1a] resulted in a substantial loss of the desired product to the aqueous phase (Table 5, entry 1). Presumably, the presence of nitromethane had increased the partitioning of ester **5** to the organic stream, and in the current solvent system higher losses were observed. To minimize product loss and avoid the need for back extractions of the aqueous stream, we initially investigated several organic solvents in combination with aqueous solutions of Rochelle's salt. The results indicated that THF was superior to other solvents in the ability to retain the product in the organic layer (Table 5, entries 2−5). It was then possible to further reduce the product losses to the aqueous layer by using a higher concentration of salts in the aqueous layer (compare Table 5, entries 5 and 6). Therefore, utilizing a 20 wt % Rochelle salt solution reduced the product loss in the aqueous phase to 4%; however, inorganic solids precipitated from the aqueous solution after the reaction mixture was diluted with THF. The presence of these solids greatly complicated the phase split during the workup and was therefore undesirable on scale, as these solids would have to be removed via an additional operation such as a polish filtration. To resolve the challenges presented by the presence of the precipitated solids, we investigated a number of reagents which were known to have a higher solubility in water. Disappointingly, commonly utilized salts such as sodium citrate or potassium phosphates (Table 5, entries 6−11) showed unsatisfactory results, i.e., solids formed or high product losses were observed. Gratifyingly, conducting the workup with an aqueous solution of $(NH_4)_2HPO_4$, a commodity chemical[18] that has rarely been used in organic processes, was found to be optimal. Both rapid phase splits and minimal product loss were achieved. Additionally, no precipitated solids or rag layers were observed during the workup (Table 5, entries 12−13).

Table 5. Optimization of the Aqueous Workup Procedure

entry	conditions[a]	phase separation	loss in aqueous phase (%)
1	THF, 15% Na_2SO_4	rag layer	8
2	MeTHF,15% Rochelle salt	product partially precipitated out	N.D.[b]
3	MeCN, 15% Rochelle salt	product partially precipitated out	N.D.
4	EtOAc, 15% Rochelle salt	product partially precipitated out	N.D.
5	THF, 15% Rochelle salt	rag layer	12
6	THF, 20% Rochelle salt	inorganic solids and rag layer	4
7	THF, 20% Na citrate	inorganic solids and rag layer	2
8	THF, 20% NH_4Cl	inorganic solids, no rag layer	10
9	THF, 20% NH_4OAc	inorganic solids, no rag layer	5
10	THF, 15% K_3PO_4	inorganic solids, no rag layer, phase moderate rate of split:	8
11	THF, 20% K_2HPO_4	inorganic solids, no rag layer, moderate rate of phase split	7
12	THF, 20% $(NH_4)_2HPO_4$	no solids, no rag layer; rapid phase split	4
13	THF, 25% $(NH_4)_2HPO_4$	no solids, no rag layer, rapid phase split	1

[a]20 volumes of the organic solvents and 10 volumes of the aqueous salt solutions were used. [b]N.D.: not determined.

As the workup conditions were defined, we turned our attention to the subsequent hydrolysis of the methyl ester **5** to acid **2** (Figure 1). The treatment of the rich organic stream from the acylation reaction with NaOH (1 N, 4.5 equiv) cleanly furnished the desired acid **2b** in 3 h. However, solid sodium oxalate was occasionally formed in the reaction mixture, presumably due to high levels of oxalic acid carried over from the Friedel−Crafts acylation which utilized an excess of methyl chlorooxalate. The presence of these solids in the process stream was undesirable since they complicated the subsequent phase separation. This issue was resolved by switching the base for the hydrolysis from NaOH to KOH because the resulting potassium oxalate has increased solubility in water, and therefore, no solids were observed during the hydrolysis.

With the completion of the initial two chemical transformations, namely, Friedel−Crafts acylation of azaindole **1** and subsequent methyl ester hydrolysis to yield acid **2b**, our last task prior to the coupling to form amide **3** was to isolate acid

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2b. Due to the ionizable nature of **2b**, we were able to isolate it by protonation with strong acids to form an amine salt or as the free acid with more controlled addition of mineral acids. Attempts to isolate the product as a metal carboxylate salt at high pH were unsuccessful. In the amine salt approach, a strong acid (pK_a < 1) was required due to the weak basicity of 6-azaindole **2b**. Among the common strong acids (sulfonic acids, HCl, etc.), only HBr provided a crystalline salt **2a** that was amenable to isolation. However, the quality of the resulting HBr salt was inconsistent in terms of color and potency, which detrimentally impacted the subsequent amide coupling step. On the other hand, on the basis of the calculated pK_a (2.6) of acid **2b**, a number of acids were identified that would be capable of neutralizing the basic hydrolysis stream and to produce crystalline free acid **2b**. By judicious choice of the acid used for the neutralization, we could also prevent over protonation of the product, and the isolation challenges associated with this, in the case of an overcharge of the acid because the small differences in pK_a would preclude this from occurring. This adds an element of robustness to the isolation procedure. Among the viable acids that met the pK_a requirements, phosphoric acid was preferred over carboxylic acids, such as tartaric, citric, and malonic acids, since carryover of any residual carboxylic acids would potentially interfere with the subsequent amidation. Additionally, it was found that an improved particle size distribution was obtained with the controlled addition of a 25% w/w aqueous solution of H_3PO_4 at 60 °C, leading to better filtration rates (>650 L/m^2 h) during the isolation of carboxylic acid **2b**. In practice, **2b** was isolated in following manner: the rich aqueous stream post hydrolysis was acidified with 25% H_3PO_4 at 60 °C until the pH of the batch reached 2.9−3.1; the batch was then seeded with 0.5 wt % **2b**, and H_3PO_4 addition continued until the pH of the batch was below 2.5. After cooling to 20 °C, filtration of the resulting slurry afforded the product.

During our optimization of the hydrolysis step, we observed the formation of a truncated acid impurity **7** (Figure 2) which

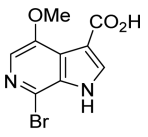

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Figure 2. Truncated acid impurity **7**.

we typically saw at low levels (0−3 AP) in the process streams. In particular, we noted that, when the hydrolysis was carried out with older lots of KOH, higher levels (3 AP) of the impurity were formed. Further investigation indicated that the treatment of ester **5** with potassium carbonate resulted in the formation of even greater amounts of the truncated acid **7** (~8 AP). We surmised that the older lots of KOH were contaminated with carbonates, presumably due to absorption of CO_2 from the atmosphere, and the presence of the carbonates during the hydrolysis resulted in the formation of this impurity.[19] Therefore, the use of KOH with minimal exposure to the atmosphere was required to ensure that the formation of impurity **7** was minimized.

Very gratifyingly, the acylation and hydrolysis chemistry has been demonstrated on scales up to 80 kg of 6-azaindole **1** input, providing **2b** in high yields (82−88%) and excellent quality (>99.5 AP, >98 wt %). Having overcome the major challenges associated with the reaction, workup and isolation of **2b**, we were now well-poised to focus our attention on the subsequent amidation chemistry to prepare intermediate **3**.

Amidation. Our early development efforts toward a scalable amidation reaction occurred concurrently with the development of the process to prepare **2b**, and early amidation development work utilized the HBr salt **2a** (Scheme 3). A screen of reaction conditions to couple acid **2a** and piperazine **4a** identified a number of viable coupling reagents capable of promoting the desired transformation (Table 6). While all of the reagents examined provided the desired product with good purity, complications were observed with several of our initial approaches. The use of EDCI[20] afforded the desired product, but initial studies required column chromatographic purification of **3** and resulted in low yield. Oxalyl chloride[21] (Table 6, entry 2) proved to be a competent reagent for the desired transformation; however, high levels of the C7-chloride impurity **8** (Figure 3) were observed with extended reaction times. This lack of a suitable hold point led us to explore CDI,[3c,d] which proved to be a good reagent for the

Table 6. Comparison of Amidation Agents Screened To Prepare Amide 3

entry	coupling agent	yield (%)	AP	wt %
1	EDCI[a]	31	99.6	96.0
2	oxalyl chloride[b]	75−85	99.2	97−99.5
3	CDI[c]	85	98.9	91.9
4	T3P[d]	>80	99.1	98.2

[a]The following reaction conditions were used. 1.2 equiv of EDCI, 3 equiv of DIPEA in DCM at 0−25 °C. [b]1.5 equiv of oxalyl chloride, 3.5 equiv of DIPEA in DCM at 0−25 °C. [c]1.1 equiv of CDI in DMF at 10 °C. [d]1.3 equiv of T3P, 4.4 equiv of DIPEA in acetonitrile at 5−25 °C.

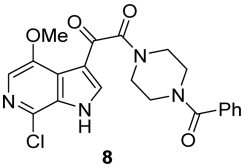

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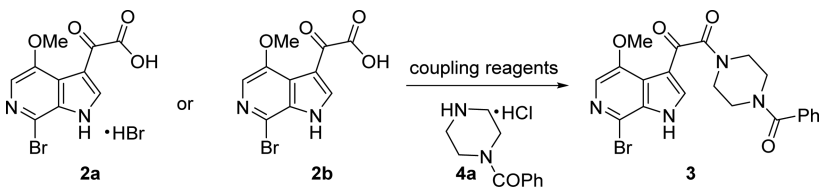
Figure 3. Structure of the C-7 chloro impurity **8**.

Scheme 3. Transformation of Acid 2a or 2b to Amide 3



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transformation, affording the desired product in 98.9 AP purity and 85% isolated yield (Table 6, entry 3). CDI was utilized in early scale-up efforts and delivered material of acceptable quality to support downstream development efforts. However, the isolated product contained low levels of imidazole, leading to reduced potencies of amide **3**. The use of CDI was also a two-stage process which required activation of the carboxylic acid prior to the charge of amine **4**; however, it was found that the acyl imidazole intermediate was not stable at the reaction temperature. This instability caused some concerns for continued scale up work and because we wished to streamline the process additional coupling reagents were investigated. It was subsequently determined that comparable yields and good purity could be obtained using *n*-propylphosphonic anhydride (T3P),[22] which did not require preactivation of acid **2a** (Table 6, entry 4).

The optimization of the reaction utilizing T3P began by screening the equivalents of the reagent, base, reaction solvent, and temperature. It was quickly determined that the reaction temperature and the addition rate of the T3P needed to be controlled to avoid localized heating within the reaction mixture.[23] Ultimately, the optimized reaction conditions included cooling a mixture of acid **2a**, 1.4 equiv of piperazine hydrochloride **4a**, and 4.5 equiv of DIPEA in acetonitrile to 5 °C. T3P was charged to this mixture over 30−60 min, and then the reaction was warmed to 20−25 °C and held until the acid **2b** level was <1 AP. Subsequently, we developed an efficient protocol to isolate amide **3**, which included an initial charge of two volumes of water to the reaction mixture. The mixture was then seeded and aged, and finally an additional eight volumes of water as antisolvent were added over 3 h. The resulting slurry filtered rapidly and was washed with a mixture of acetonitrile/water to provide the desired amide in high yield and purity.

The procedure that utilized T3P provided multiple benefits over our previous CDI process, such as improved yield (94% on 109 kg scale), higher purity (99.5 AP), a significant reduction in cycle time, and ultimately a much more robust process. While the acyl imidazole intermediate in the CDI process was unstable at the reaction temperature and resulted in variable quality of the product on scale, the procedure utilizing T3P provided consistent results.

Despite the excellent results observed with the T3P process, concerns regarding its cost, patent status, and availability from a limited number of suppliers drove the development of an alternate approach based on diphenylphosphinic chloride (DPPCl).[24] The latter reagent can be obtained from multiple sources and was expected to allow us to perform a similar single pot, all-in transformation.[25]

During initial studies of the DPPCl mediated amidation process, a mixture of acid **2a** and 1.4 equiv of piperazine **4a**, and 4.0 equiv of DIPEA in acetonitrile was treated with 1.7 equiv of DPPCl.[26] By switching to DPPCl, we encountered a challenge with the complete removal of the byproduct diphenylphosphinic acid (DPPOH) from the isolated product **3**. To control the amount of the acidic DPPOH present in the dry cake, 1.8 equiv of sodium hydroxide was added to the aqueous quench. The material was then isolated by filtration of the resulting slurry after the aqueous quench. Initially this approach appeared promising, resulting in only a 5−8% loss of amide **3** in the mother liquor and consistently producing isolated material with ∼0.1 AP of DPPOH when the quench and isolation was completed within 2 h (Table 7, entry 1). Unfortunately, during additional experiments, the high variability in both isolated yield and level of residual DPPOH in **3** was observed when the quench times were extended.

Table 7. Variable Isolated Yield of 3 and DPPOH Level in the Initial Experiments

entry	quench reagent	quench time	isolated yield (%)	mother liquor loss (%)	DPPOH (AP)
1	NaOH, H_2O	2 h	90−92	5−8	0.1
2	NaOH, H_2O	18 h	48	44	0.1
3	H_2O	18 h	86−90	3	0.1−41.4
4	H_2O, DPPOH seeds	72 h	89	3	1.1

A detailed study of the process hold points at this stage indicated that an increase in the time taken to perform the quench resulted in an increase in the amount of product lost to the mother liquors, with as much as 44% being lost if the time for the quench was extended to 18 h (Table 7, entry 2). A possible explanation for this time dependent increase in product loss to the mother liquors was a slow equilibration that resulted in the formation of the ammonium salt of DPPOH and the sodium salt of amide **3** (Scheme 4), both of which have high solubility in acetonitrile/water mixtures. To circumvent this issue, we opted to utilize an aqueous quench with no additional base. While this approach consistently provided low mother liquor loss and high isolated yields (Table 7, entry 3), the amount of residual DPPOH was once again highly variable, with levels in the isolated product reaching as high as 41 AP. Initially we believed that the precipitation of a small amount of the DPPOH led to further crystallization of DPPOH, but attempts to reproduce this phenomenon by seeding the reaction mixture with DPPOH were unsuccessful. For example, when the mixture was seeded with DPPOH (1 wt % of the input), no evidence of additional precipitation was observed, even after 72 h (Table 7, entry 4).

While our initial hypothesis regarding DPPOH solids inducing further crystallization proved incorrect, a further investigation of the reaction revealed that the main variable between product containing low versus high levels of DPPOH was the lot of acid **2a** used. This led us to consider the possible differences between the batches of the acid **2a** we were studying. We quickly discovered that the total amount of the HBr present in the isolated material was inconsistent from batch to batch. We had determined that DPPOH was soluble at pH values >4, and monitoring the pH over the course of the crystallization showed that the final pH also varied with different inputs of **2a**. We were able to demonstrate a strong correlation between final pH of the crystallization media and the levels of DPPOH in the isolated solids. The observed variation in the final pH of the crystallization was attributed to the inconsistent formation of the HBr salt of acid **2a** during its isolation. As discussed previously, since we had improved the isolation of **2b** by quenching the hydrolysis stream with phosphoric acid and would be isolating the free acid **2b**, we expected to circumvent this issue in future reactions.[27]

An additional study performed using the free acid **2b** under the DPPCl conditions was conducted, and the final pH during the crystallization of **3** (Table 8) was determined for experiments using different quantities of DIPEA. As expected, 2.0 equiv of DIPEA resulted in a low final pH at the crystallization end point and high levels of DPPOH in isolated amide **3** (Table 8, entry 1). Furthermore, the reaction did not go to completion even after 72 h. The use of 3.0 equiv of

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Scheme 4. Slow Formation to the Soluble Sodium Salt of Amide 3 and Ammonium Salt of DPPOH

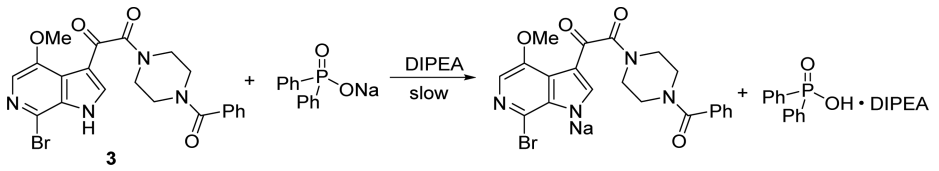

Table 8. Correlation of the Equivalents of DIPEA with Yields (3) and DPPOH Levels

entry	DIPEA (equiv)	pH, mother liquor	isolated yield (%)	DPPOH (AP)	mother liquor losses of 3 (%)
1	2.0	1.14	56	45.1	1.7
2	3.0	2.81	91	35.1	1.8
3	4.0	3.29	84	0.19	2.6
4	5.0	8.95	74	0.16	15.7
5	6.0	9.57	42	0.46	50.2

DIPEA (Table 8, entry 2) appeared to be the minimum amount of base required for reaction completion, but the final pH observed in the crystallization media was still low, and high levels of DPPOH (35.1 AP) were present in the dry cake. When we increased the amount of DIPEA to 5.0 and 6.0 equiv (Table 8, entries 4 and 5), we observed very low levels of DPPOH (<1 AP) in isolated **3**, but high product losses to the mother liquor of 15.7 and 50.2%, respectively. It appears that at a pH level of 9 or higher, significant deprotonation of the azaindole of product **3** results in the formation of a soluble salt which increases the losses to the mother liquor. We determined that the optimal charge of DIPEA was 4.0 equiv, with a narrow acceptable range of 3.8−4.1 equiv to obtain amide **3** in both high purity and high yield. These findings were of significant concern regarding the scalability of this crystallization to avoid sacrificing either yield or product purity. Too little base would result in the contamination of the dry cake with DPPOH, whereas too much base would result in high mother liquor losses. While we determined that the product could be recovered as a second drop from the mother liquor through careful adjustment of the pH, we wanted to avoid this additional operation and therefore concluded that DIPEA was not the optimal base for this transformation as it did not afford us the necessary process robustness.

Because of the concern around a narrow acceptable range for the base charge in the amidation process, we explored the possibility of changing the base to achieve a more robust process. As shown in Table 9, the pK_a of the base significantly impacted the mother liquor losses and the isolated yields of product **3**. The ideal base needed to be sufficiently weak so as not to deprotonate azaindole **3** thereby avoiding high mother liquor losses; however, the base also needed to be strong enough to buffer the solution and keep the DPPOH byproduct solubilized. The hypothesis that the strength of the amine base could impact the isolated yield of **3** was confirmed when we tested *N*-methylmorpholine (NMM) in the reaction (entry 5, Table 9). With a moderate pK_a of 7.4 for its conjugate acid,[28] we could use four to six equivalents of NMM and obtain consistent mother liquor losses of <5%. The quality of the product was consistently >98 AP and 98 wt % with <1 AP DPPOH observed in the isolated solid.

Table 9. Effect of Various Bases on the Mother Liquor Loss and the Isolated Yield of 3

entry	base, 5 equiv	pK_a	mother liquor losses of 3 (%)	isolated yield	DPPOH (AP)
1	DIPEA	11.4	15.7	74	0.16
2	*cis*-2,6-dimethylpiperidine	10	6.3	76	0.20
3	*N*-methylpiperidine	10.1	7.6	N.D.[a]	N.D.
4	DBU	12	>20	N.D.	N.D.
5	NMM	7.4	3	91	0.35

[a]N.D.: not determined.

Throughout the development of the DPPCl process, we had observed two additional DPPCl related in-process impurities (Figure 4). Phosphoramide **9** was formed from a side reaction between excess DPPCl and piperazine **4**. Fortunately, because DPPCl reacts faster with acid **2b** than with piperazine **4**, the formation of this impurity could be controlled by the equivalents of DPPCl used in the reaction. Phosphate **10** was formed from the reaction of DPPCl with residual phosphate (H_3PO_4/KH_2PO_4) present in acid **2b** originating from the workup and isolation process of this compound. With the improved NMM process, we began to observe higher levels (up to 3 AP) of side product **10** in the process stream. This was likely due to the buffered reaction pH giving rise to increased levels of dibasic phosphate in the reaction stream. Fortunately, both impurities **9** and **10** were purged effectively during the crystallization and isolation of **3**, and only low levels were observed in the dry cake.

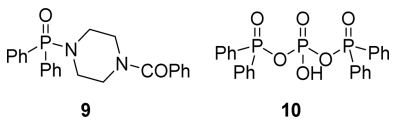

Figure 4. Major in-process impurities in the DPPCl process.

While we had developed an efficient process for the preparation of amide **3** using DPPCl and NMM in acetonitrile, we were concerned about the slurry-to-slurry nature of the process.[29] To better understand the mass transfer phenomena of this reaction, we initiated studies on the effect of agitation rate on the reaction performance. Typical reaction conditions in a 1 L reactor with an agitation rate of 250−300 rpm gave the desired product in 95% isolated yield. However, when the agitation rate was reduced to 50 rpm, a sharp erosion in the isolated yield to 58% was observed and the mass balance was poor with the mother liquor containing <5% of the product. This low yield was not due to incomplete reaction, as analysis indicated that acid **2b** was completely consumed. The yield could not be improved by increasing the agitation after the initial age, by increasing the age time of the reaction, or by the addition of a second charge of DPPCl. Interestingly, a full equivalent of DPPOH was present in the reaction mixture even when the water content of the reaction mixture was low, as observed by ^{31}P NMR. This suggested that the activated

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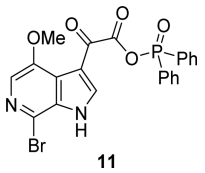
intermediate **11** (Figure 5) had been formed and subsequently reacted further to produce the full equivalent of DPPOH as a

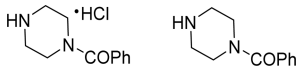


11

Figure 5. Proposed activated intermediate **11**.

byproduct, though N-phosphorylation/hydrolysis could not be eliminated as a possibility. Attempts to detect **11** by ^{31}P NMR were unsuccessful, suggesting that the intermediate was being consumed rapidly on the NMR time scale. Because no other impurities were observed by HPLC, we hypothesized self-condensation occurred at a nucleophilic center of the 6-azaindole of one molecule with the activated acid moiety of a second molecule. When the reaction was performed in the absence of the piperazine coupling partner **4**, acid **2b** was consumed, and a red, insoluble solid was isolated, further supporting the hypothesis that another molecule of the azaindole was reacting with the activated intermediate **11**. We were unable to obtain complete characterization of the red solid. However, when it was heated in the presence of aqueous sodium hydroxide, slow dissolution was observed with the simultaneous formation of acid **2b** as detected by HPLC, providing additional support for our proposal.

Consumption of **2b** and formation of the red solid had not been observed with the DIPEA process; therefore, we wanted to understand why NMM led to a higher risk of this undesired side reaction and, in turn, the potential for significant material loss. Because piperazine **4** is purchased as the HCl salt **4a**, the base used is critical to sequestering the HCl and allowing for the free base **4b** (Figure 6) to be available for the reaction. In



4a **4b**

Figure 6. Structures of piperazine **4a** (HCl salt) and **4b** (free base).

acetonitrile with 5.0 equiv of DIPEA, the concentration of **4b** was 43.5 mg/mL; however, with 5.0 equiv of NMM the concentration was only 3.3 mg/mL. Free acid **2b** was completely dissolved under the reaction conditions and readily available to generate the activated intermediate **11** which would be available to react with another molecule of acid **2b** that was in solution if no piperazine **4b** was present. On the other hand, because activated intermediate **11** does react rapidly with piperazine **4b**, we found that we could eliminate the undesired self-condensation by charging DPPCl slowly over 2 h, which ensured that there was sufficient piperazine **4b** available in solution, and therefore prevent the formation of the red solid. In fact, if agitation was unexpectedly interrupted during the process, addition could also be halted circumventing the self-condensation process, building in a level of robustness that was not previously present in this amidation process.

As the issue of the self-condensation was addressed, we next focused on how to mitigate the slurry-to-slurry challenge observed when the reaction was performed in acetonitrile, which resulted in variability in the rejection of impurities and produced isolated product with a range of purities. After obtaining solubility data for the reactants and product **3**, we were encouraged by the good solubility of **2b** and **3** in NMP and by the low solubility of amide **3** in mixtures of NMP and water. Gratifyingly, we observed comparable reactivity when NMP was used in place of acetonitrile as a solvent with the same conditions developed for the reaction in acetonitrile. Table 10 shows a comparison of the two processes. In addition, the product could easily be crystallized from the reaction mixture by adding an equal amount of water and this resulted in the isolation of **3** with improved purity. In practice, the amidation reaction was performed in 10 volumes of NMP, and a thin slurry was observed at the end of the reaction. When 2 volumes of water were charged and the mixture was heated to 60 °C, a solution was observed, which enabled the development of a controlled crystallization.

Our initial crystallization conditions involved heating to 60 °C, followed by the addition of 2 volumes of water, which resulted in approximately 200% relative supersaturation (RSS). The crystallization then proceeded with seeding, followed by the addition of more water until a total of 10 volumes were added. After cooling to 20 °C, we observed excellent results in terms of recovery, purity, and mother liquor loss (Table 11, entry 1), but a very low filtration flux of ≤100 L/m^2/h. The reason for this was apparent from the small particle size of the isolated product, generally <20 μm. We began to investigate the impact of the solvent composition at both the seed point and the isolation point to determine how it affected the particle size, filtration rate, and purity profile. The variation in the final ratio of NMP to water was found to affect the yield, but not the purity, and so we initially focused on improving the filtration rates. Concern over the high relative supersaturation at the seed point causing the formation of fine particles led us to adjust the isolation conditions to compensate. Upon reaction completion, the mixture was diluted to 17 volumes of NMP, and seeding was performed after the addition of 2.5 volumes of water at 60

Table 11. Optimization of the Solvent Composition for the Crystallization[a]

entry	NMP (vol)	water at seeding (vol)	% RSS	total water (vol)	60 °C age	mother liquor losses (%)	flux (L/m^2/h)
1	10	2	200	10	<1 h	2.8	<100
2	17	2.5	30	10	<1 h	6.8	<200
3	17	2.5	30	12	3 h	5.9%	1381
4	15	2.0	30	12	6 h	5.5%	574
5	15	2.0	30	14	3 h	4.4%	491

[a]Crystallization were performed in 1 L reactor on a 20 g input scale.

Table 10. Comparison of the Amidation Process in Acetonitrile and in NMP

process	isolated yield (%)	potency (%)	AP purity	mother liquor loss (%)	DPPOH (AP)	flux (L/m^2/h)
CH_3CN	92–95	98.0–99.5	98.1–98.9	2–5	0.2–1.0	<200
NMP	97–98	>99.5	99.8	1–2	0	<100

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°C, which reduced the RSS to 30%. While the flux was still undesirably low (Table 11, entry 2), upon the examination of the isolated crystals, we were encouraged by the appearance of larger particles and agglomerates.

After considerable experimental work, we discovered that a prolonged hold at 60 °C allowed for improved control of the crystallization. Subsequently, we identified an optimal hold time of 3 h after antisolvent addition (Table 11, entry 3), which enabled control of the particle size distribution and increased the rate of desaturation which minimized mother liquor losses.

With this knowledge in hand, all that remained was to optimize the final ratio of water and NMP. To maximize reactor volume efficiency, we chose to maintain a V_{max} of 29 volumes. We found we could improve the isolated yield by increasing the percentage of water at the end of the crystallization while maintaining adequate filtration flux and ultimately settled on using a ratio of 15:14 NMP−water. The optimized conditions gave us excellent control over the particle size while maintaining product losses at <5%. Lastly, these conditions also provided excellent control over all in-process impurities, including DPPOH, phosphoramide **8**, and phosphate **9**, which were purged to <0.2 AP in the dry cake. Overall, the amidation process routinely provided amide **3** in 94% yield with a purity of 99.8 AP and a potency of >99.5 wt % and has been successfully demonstrated on a 200 kg input scale.

In conclusion, we have disclosed our development efforts that led to a scalable processes for the syntheses of acid **2b** and amide **3**. A Friedel−Crafts acylation to produce the 3-substituted azaindole **5** utilized inexpensive tetra-*n*-butylammonium bisulfate to overcome the issue of the gelling in reaction mixtures that hampered reaction conversion. This ammonium salt effectively replaced the highly energetic solvent nitromethane originally used as a cosolvent. Challenges associated with the subsequent workup of the reaction stream which contained large amounts of aluminum salts (4.5 equiv) were overcome by using an aqueous solution of $(NH_4)_2HPO_4$. Employment of this unusual phosphate salt resulted in not only a clean phase split, but also minimized product loss in the aqueous waste. We have further demonstrated the evolution of the amidation reaction to produce **3** to a single-pot, homogeneous transformation using the cost-effective and readily available coupling reagent diphenylphosphinic chloride. We have shown that this step, which combines two of our proposed starting materials, is highly reproducible and controllable in terms of yield, liquor losses, particle size, and in-process impurity rejection. These procedures have been utilized in multiple campaigns and demonstrated reproducibly on scales of up to 200 kg. Both of these processes are currently being implemented in the proposed commercial manufacturing synthesis of the drug substance, BMS-663068.

EXPERIMENTAL SECTION

General. Solvents and reagents were purchased from commercial sources and were used as received without purification. Reactions were performed under a nitrogen atmosphere and monitored by reverse-phase HPLC on a Shimadzu chromatograph. HPLC purity refers to chromatographic area percentage. NMR spectra were recorded on a Bruker 400 spectrometer, and the chemical shifts were reported in ppm with the solvent resonance as the internal standard (^{1}H, DMSO-d_6: 2.50. ^{13}C DMSO-d_6: 39.5).

Friedel−Crafts Acylation and Hydrolysis. $AlCl_3$ (164 kg, 1230 mol; 4.6 equiv) was added to a reactor containing DCM (492 kg) under a nitrogen atmosphere. The resulting slurry was cooled to 0−5 °C, and methyl oxalyl chloride (76.5 kg, 624 mol; 2.3 equiv) was added, followed by tetra-*n*-butylammonium bisulfate (31.5 kg, 92.8 mol; 0.35 equiv) at 3−15 °C. The charging device was rinsed with DCM (50 kg), and the rinse was added to the batch. Azaindole **1** (77.8 kg, 96.4 wt %, 266 mol; 1.0 equiv) was then added in two equal portions at <15 °C. The charging device was rinsed with DCM (50 kg), and the rinse was added to the batch. The resulting mixture was held at 0−5 °C until the reaction was considered complete by HPLC analysis (AP ratio of **1** to the sum of **2b** and **5** ≤1.0%; 10−17 h). The reaction mixture was then quenched by the addition of the batch to a mixture of THF (1000 kg) and 20% aqueous solution of $(NH_4)_2HPO_4$ (937 kg) over a period of 3 h at <35 °C. The quenching mixture (600 L) was cycled to the reaction vessel until all solids were dissolved in the vessel prior to the phase separation. The resulting ester intermediate in the top organic phase was subjected to hydrolysis by the addition of aqueous KOH solution (67.5 kg in 851 kg of water) at <25 °C. After completion of the hydrolysis (3 h), the phases were allowed to separate. The aqueous layer containing the potassium salt of the product **2b** was warmed to 60−65 °C and acidified by addition of 25% phosphoric acid until the pH of the mixture was ≤3.0 (417 kg of acid, pH 2.84). The seed of **2b** (375 g) was then added, and the batch was held for 1−2 h at 60−65 °C before further acidified by the addition of a 25% H_3PO_4 solution until a pH ≤2.5 was observed (208 kg, pH 2.4). The resulting slurry was agitated at 60−65 °C for 1−2 h, then cooled to 20−25 °C over a period of 3−5 h. The slurry was aged until the product concentration in the supernatant was ≤0.10 wt % (6 h), and then the batch was filtered. The reactor was rinsed with water (375 kg), and the rinse was applied as a cake wash. The filter cake was further washed with water (375 kg) and acetonitrile (149 kg), and dried in vacuo at 40−50 °C until LOD was ≤1.0%. A total of 70.4 kg of acid **2b** was collected as light yellow solids in 87.2% yield (98.7 wt %, 99.6 AP). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.64 (s, br, 1 H), 13.03 (s, 1 H), 8.35 (s, 1 H), 7.82 (s, 1 H), 3.92 (s, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 182.8, 166.2, 149.9, 137.6, 133.0, 123.6, 121.6, 116.8, 114.0, 56.2. HRMS $[M + H]^+$ calc. for $C_{10}H_8BrN_2O_4$: 298.9667; found: 298.9668.

Amidation. Acid **2b** (69.2 kg, 98.7 wt %, 228 mol; 1.0 equiv) was added into a reactor containing NMP (641 kg), followed by piperazine **4a** (67.2 kg, 296 mol; 1.3 equiv) at 20−25 °C under a nitrogen atmosphere. The addition device was rinsed with NMP (35.4 kg), and the resulting rinse was added to the batch. NMM (117 kg, 1140 mol; 5 equiv) was charged next, followed by a rinse of NMP (17.7 kg). The mixture was agitated for 1 h at 20−25 °C and then cooled to 0−5 °C. DPPCl (75.5 kg, 281 mol; 1.2 equiv) was added over a period of 2−3 h at <15 °C, followed by a rinse of NMP (17.7 kg). The reaction mixture was warmed to 20−25 °C and aged until the reaction was determined to be complete by HPLC analysis (AP ratio of **2** to **3** ≤1%; 1−2 h). A mixture of NMP (356 kg) and water (173 kg) was then charged at 20−35 °C. After warming to 55−60 °C, the batch was seeded with 682 g of amide **3**, and water (21.0 kg) was used to rinse the charging line; then the rinse was added to the batch. After mixing for 1 h, water (810 kg) was charged to the batch at 55−60 °C, and the resulting slurry was agitated for 3−4 h. The batch was then cooled to 20−25 °C over a period of 3−4 h and held until the concentration of amide **3** in the supernatant was ≤0.25 wt % (20 h). The resulting slurry was filtered, and the reactor was

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rinsed with a mixture of water/NMP (107/104 kg). The rinse was used as a cake wash. The filter cake was further washed with water (208 kg) and acetonitrile (163 kg) and dried in vacuum at 40−50 °C until LOD was <0.5%. A total of 102 kg of amide **3** was collected as an off-white solid in 93.7% yield (99.8 AP; 98.6 wt %). The spectra data of this material were identical to those previously reported.[1a]

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Notes

The authors declare no competing financial interest.

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(7) The acylation was also investigated in other solvents. For example, the reactions proceeded well (>95% conversion) as homogeneous mixtures in DCM/nitrobenzene (1:1; a total of 10 volumes) or DCM/nitropropane (7:3; a total of 10 volumes). However, neither of the two nitro solvents is preferred on scale. The acylations in the other solvents, such as chlorobenzene or trifluorotoluene, led to low conversions and gelling mixtures.

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(15) During the preparation of this manuscript, a new method for C3-dicarbonylation of indoles was reported via an oxidative coupling with methyl ketones; see: Gao, Q.; Zhang, J.; Wu, X.; Liu, S.; Wu, A. *Org. Lett.* **2015**, *17*, 134.

(16) It is known that ionic liquids promoted acylation; see: Yeung, K.-S.; Qiu, Z.; Farkas, M. E.; Xue, Q.; Regueiro-Ren, A.; Yang, Z.; Bender, J. A.; Good, A. C.; Kadow, J. F. *Tetrahedron Lett.* **2008**, *49*, 6250 and references therein. However, the acylation of **1** with the ionic liquid resulted in formation of a gel..

(17) The initial motivation behind removing nitromethane from the acylation process was to avoid using a highly energetic solvent on large scale. Additionally, our early efforts to streamline the acylation hydrolysis process into a telescope were complicated by the presence of the nitromethane. Since the bases used for the hydrolysis, such as NaOH or KOH, largely deprotonate nitromethane, a large excess of base (>30 equivalents) was necessary to drive the hydrolysis reaction to completion in the presence of nitromethane. Additionally the deprotonation of nitromethane led to dark reaction streams, resulting in an issue of colored isolated product. To avoid these challenges, a tedious azeotropic removal of the nitromethane was conducted prior to hydrolysis. Overall, replacement of the nitromethane cosolvent with the Bu_4NHSO_4 not only resulted in a safer reaction that was more amendable to scale-up, it also greatly streamlined the processing by avoiding the necessary azeotropic removal of nitromethane.

(18) This ammonium phosphate is inexpensive and used as a fertilizer and a fire retardant.

(19) We found that the treatment of acid **2b** with an aqueous solution of potassium/sodium bicarbonate or carbonate produced several AP of impurity **7**, while the treatment with KOH or NaOH aqueous solution did not generate the impurity.

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(22) For an example of an amidation process using T3P, see: Dunetz, J. R.; Berliner, M. A.; Xiang, Y.; Houck, T. L.; Salingue, F. H.; Chao, W.; Yuandong, C.; Shenghua, W.; Huang, Y.; Farrand, D. *Org. Process Res. Dev.* **2012**, *16*, 1635.

(23) Reactions at higher reaction temperatures resulted in more impurities.

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(26) The addition rate of DPPCl to the reaction mixture had to be carefully controlled due to the substantial exotherm that was encountered. Under the current conditions, the heat flow commenced within 5 min of the start of the DPPCl charge and rose to a steady rate in 10 min, and was maintained over the remaining addition time. No delayed exotherm or accumulating heat was observed. Thermal conversion was measured at 95% with an adiabatic temperature increase of 12 °C.
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