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Preparation of the HIV Attachment Inhibitor BMS-663068. Part 5. Selective C-7 Bromination of the 6-Azaindole Core

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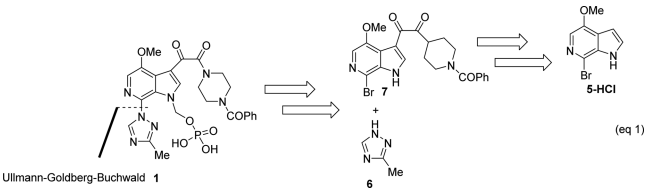
ABSTRACT: We report research focused on the preparation of an advanced intermediate in the synthesis of a novel antiretroviral. This manuscript describes the development of an efficient oxidation of a 6-azaindole derivative, the bromination of the resulting *N*-oxide using PyBroP, the removal of the protecting group, and the isolation of the brominated azaindole product. The work reported herein has been successfully implemented in the multikilogram scale to fund development and clinical activities of BMS-663068.

INTRODUCTION

The regioselective incorporation of the 3-methyl-1,2,4-triazole into the 7 position of the azaindole core is one of the chief challenges in the synthesis of BMS-663068 (**1**). After considerable effort, this was efficiently achieved by using a copper-catalyzed Ullmann−Goldberg−Buchwald coupling reaction between the functionalized azaindole **7** and triazole **6** (eq 1).[1] Selective installation of the bromide into the **7** position



of the heterocyclic core is a key transformation toward successfully reducing this synthetic strategy to practice. Herein, we describe the preparation of the brominated azaindole **5** according to the following three-step telescope sequence: (a) *N*-oxidation of a *N*-benzenesulfonyl protected 6-azaindole (**2**); (b) regioselective bromination of the resulting *N*-oxide (**3**), and (c) deprotection of the benzenesulfonyl group followed by isolation of the hydrochloride salt **5** (Scheme 1).

Due to the mutagenic and highly energetic nature of *N*-oxide **3**, we decided to telescope these three steps to avoid its isolation and handling. In addition, **5** proved to be the optimal intermediate for isolation due to exceptional purging of reagent and process related impurities.

RESULTS AND DISCUSSION

Oxidation. Initially, the *N*-oxidation of **2** was conducted using a catalytic methyltrioxorhenium (MTO) and hydrogen peroxide urea complex (UHP) in dichloromethane.[1−3] Although the procedure provided the product in excellent yield and quality, high raw material costs made it inadequate for large-scale implementation. To define new oxidation conditions, we evaluated a range of oxidants and solvents with the following criteria in mind: (a) reagent and process safety; (b) robustness; (c) cost effectiveness, and (d) facile workup with a minimal number of unit operations. Selected results from the evaluation of oxidants are presented in Table 1.[4]

Both *m*-CPBA[5] and the combination of Ac_2O/H_2O_2[6] provided excellent conversion and product quality, but both required lengthy work-ups to eliminate the carboxylic acid byproducts that were detrimental to the performance of the subsequent bromination reaction. A mixture of phthalic anhydride and H_2O_2[7] provided an optimal balance between reactivity and ease of removal of the byproducts via a single aqueous wash under basic conditions (pH > 8).[8] Using this combination of reagents, we carried out the oxidation with phthalic anhydride (1.2 equiv) and aqueous H_2O_2 (30−35%) (1.4 equiv) in CH_2Cl_2 at 35 °C. Upon reaction completion the mixture was treated with an aqueous solution combining Na_2SO_3, to reduce excess peroxide, and aqueous K_3PO_4, to extract the carboxylic acid byproducts into the aqueous layer. An additional aqueous wash was conducted to remove inorganic residues. After the aqueous workup, a solvent exchange to toluene via distillation provided *N*-oxide **3** as a crystalline solid in 85% yield and >99 area % purity.

An analysis of compound **3** revealed safety concerns that prompted us to avoid its isolation on larger scale. *N*-Oxide **3** was found to be thermally unstable with a high decomposition energy (−838 J/g with T_{AD} of 419 °C) and an onset temperature of 103 °C in the solid form. In addition, **3** tested positive in the bacterial reverse mutation assay (AMES).[9] Consequently, we decided to perform the bromination step using the intermediate *N*-oxide **3** as a process stream in toluene.[10]

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Scheme 1. Synthesis of 7-Bromo-4-methoxy-1*H*-pyrrolo[2,3-*c*]pyridine Hydrochloride (5-HCl)

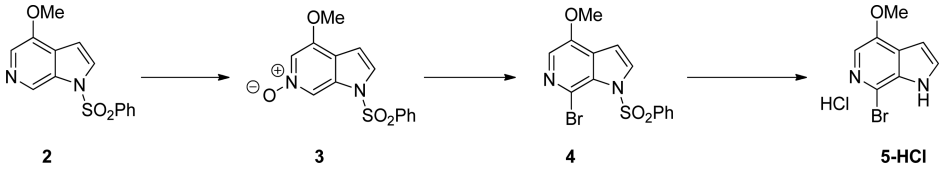
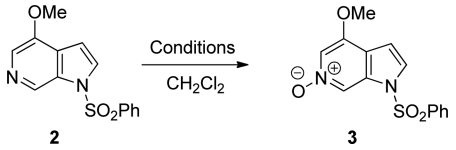


Table 1. Selected Conditions for the Oxidation of Azaindole 2



conditions	area % of *N*-oxide 3[a]	observations
MTO (cat)/UHP	96.3	high cost
m-CPBA	97.9	intensive workup
Ac_2O/H_2O_2	98.0	intensive workup, potential safety issues
phthalic anhydride/ H_2O_2	98.7	safe, economical, simple workup

[a]Area % of reaction mixture based on HPLC integration at 230 nm.

The initial scale-up of the oxidation revealed variability in the yield (75−95%) as well as poor mass balance for the reaction and workup.[11] To further assess the origin of these processing issues, we conducted a detailed evaluation of the product stability in the presence of all the reaction components. These experiments revealed that *N*-oxide **3** decomposes in the presence of aqueous H_2O_2 and that the extent of the decomposition is pH dependent (Table 2). At higher apparent pH the decomposition was more significant, suggesting that the nucleophilic hydrogen peroxide anion could be responsible for the lack of stability.[12]

Table 2. Stability of the *N*-Oxide 3 towards Hydrogen Peroxide as a Function of Additive

conditions[a]	mol % 3
H_2O_2 + phthalic acid	99%
H_2O_2 + K_2HPO_4	85%
H_2O_2 + K_3PO_4	55%

[a]*N*-oxide **3** was exposed to H_2O_2 in a representative biphasic mixture of DCM/H_2O at 25 °C for 19 h

We reasoned that adjusting the procedure to minimize the exposure of *N*-oxide **3** to excess peroxide during the reaction and workup should address both the yield variability and mass balance issues. First, the stoichiometry of H_2O_2 and phthalic anhydride were modified (Table 3). Second, aqueous H_2O_2 was slowly added over 2 h to a 35 °C solution of azaindole **2** in CH_2Cl_2. Under these conditions, fast consumption of H_2O_2 prevented the exposure of *N*-oxide **3** to excess peroxide, as evidenced by the rate of product formation matching the rate of H_2O_2 addition (Figure 1).

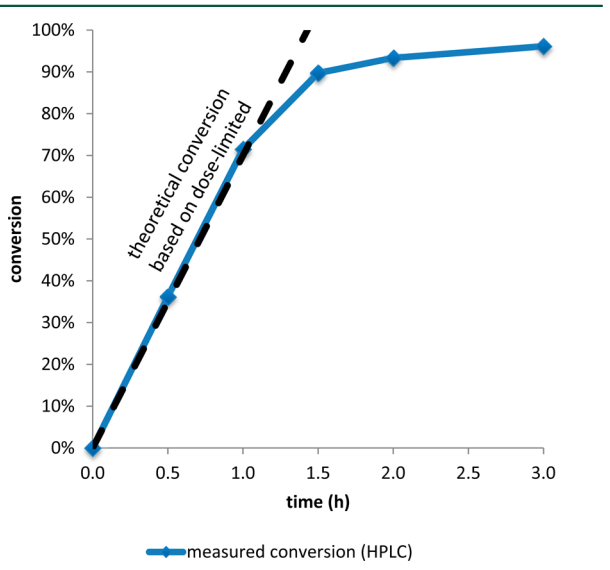


Figure 1. Rate of formation of **3** with the slow addition of H_2O_2 at 35 °C. The dotted line shows the theoretical conversion based on the addition of H_2O_2.

Finally, the aqueous workup was also modified. The original quench procedure involved the addition of a mixture of aqueous Na_2SO_3 and K_3PO_4 to the reaction vessel to minimize unit operations and cycle time. However, the presence of K_3PO_4 before the complete quench of excess peroxides could cause product decomposition and yield loss (Table 2). The workup was modified by adding the aqueous Na_2SO_3 first to reduce excess peroxides, followed by the basic aqueous solution to ensure the carboxylic acid byproduct was extracted into the aqueous layer. Collectively, these modifications allowed for reproducible performance across a range of scales, increased the yield of the oxidation, and eliminated the variability (Table 3).

Bromination. Having a suitable oxidation procedure in place, we sought to optimize the bromination step of the telescoped process. The discovery of PyBroP[13,14] as an effective brominating agent for compound **3**[1] was crucial to enable the synthesis of BMS-663068.[15] The major challenge to this bromination reaction was the competitive formation of byproduct **2**, which negatively impacted the yield of the transformation (Scheme 2).[16,17]

At the outset, we sought to scale up the bromination using K_3PO_4 as the base and trifluorotoluene as the solvent as

Table 3. Comparison between the Initial and the Modified Oxidation Processes

process	H_2O_2 addition	H_2O_2 (equiv)	anhydride (equiv)	aqueous quench	solution yield
initial	uncontrolled (20 °C)	1.4	1.2	Na_2SO_3 *and* K_3PO_4	85 ± 10%
modified	120 min (35 °C)	1.2	1.3	Na_2SO_3 *then* K_3PO_4	90 ± 3%

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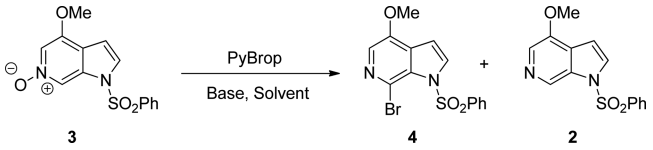
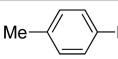
Scheme 2. Major Products of the Bromination of *N*-Oxide 3 with PyBroP



identified in the proof of concept studies.[1] Although this procedure worked well in the laboratory, it posed a significant challenge for a larger scale as the particle size of the base was critical to achieve acceptable reaction rates.[18] Obtaining K_3PO_4 on the large scale with the desired powder properties proved unfeasible and provided an undesirable source of variation in the reaction.[19] We therefore evaluated alternative bases and solvents and identified *N*,*N*-dimethyl-*p*-toluidine and *N*,*N*-diisopropylamine (DIPEA) as suitable replacements (Table 4).

Table 4. Selectivity of the Bromination of *N*-Oxide 3 with PyBroP and Selected Bases

Entry	Base	Solvent	Ratio of **4**:**2**[a]
1	K_3PO_4	Ph-CF_3	8 : 1
2		Ph-CF_3	6 : 1
3	DIPEA	Toluene	4 : 1

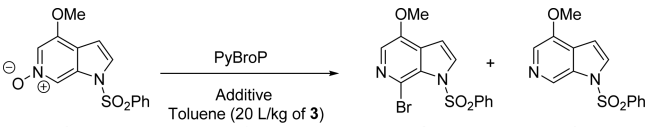
[a]Ratio of bromination to deoxygenation byproduct determined by ^{1}H NMR. 100% conversion obtained for each reaction.

Considering the availability and cost of DIPEA and toluene, we initially used these conditions (entry 3, Table 4), despite the lower yield resulting from the lower selectivity of the reaction. The undesired product **2** could be purged to acceptable levels during downstream processing. These conditions were used to prepare 293 kg of brominated azaindole **5**-HCl to support critical clinical and development activities.

Subsequent to this initial campaign, the bromination reaction was further investigated to understand the experimental variables that affect the formation of the deoxygenated byproduct **2** and improve the yield of the process. As a starting point to the investigation, we considered the mechanism for this transformation (Scheme 3).

We hypothesized that compound **3** and PyBroP would first react to generate an oxyphosphorane intermediate **8** that could be involved in a dissociation equilibrium.[14] The incorporation of the bromide into the azaindole core would lead to intermediate **9**.[14a,20] Pathway A, which could be favored by an external base, would then lead to the formation of the desired brominated product **4**, whereas pathway B would form the byproduct **2**.[17] Two observations suggested that an external base might not be required for the productive bromination pathway A to occur: (a) the base concentration did not significantly impact the reaction selectivity, and (b) the reaction proceeded in the absence of an external base but stalled at approximately 50% conversion with a **4**:**2** product ratio of 7:1. Studies to understand the effect of residual water in the reaction mixture provided an important breakthrough. The addition of molecular sieves led to higher selectivities, albeit with incomplete conversion (entry 1, Table 5). Accordingly, the

Table 5. Bromination Reaction of 3 in the Presence of H_2O Scavengers

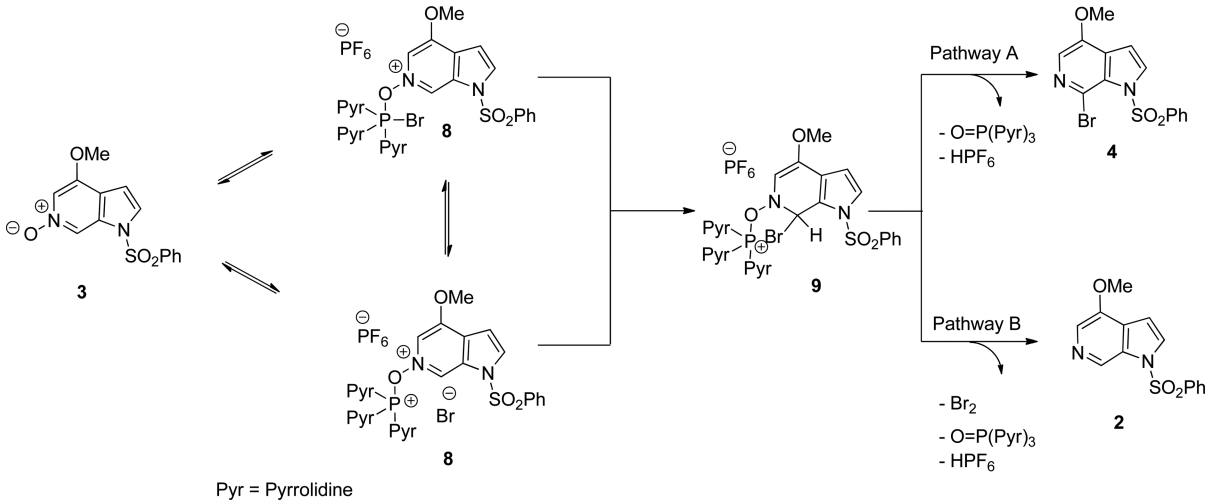


entry	additive (equiv)	conversion[a]	**4**:**2** ratio[a]
1	molecular sieves 4 Å	>80%	40:1
2	BSA (1.0)[b]	>95%	12:1

[a]Evaluated by HPLC analysis at 230 nm. [b]Reaction performed at 10 °C.

identification of compatible and readily available chemical dehydrating agents became the next development goal. Neither the dehydrating reagent, nor its byproducts, should be competent nucleophiles that could react with the *N*-oxide **3**.[14] Following this logic, *N*,*O*-bis(trimethylsilyl)acetamide

Scheme 3. Proposed Mechanism for the Bromination Reaction of 3



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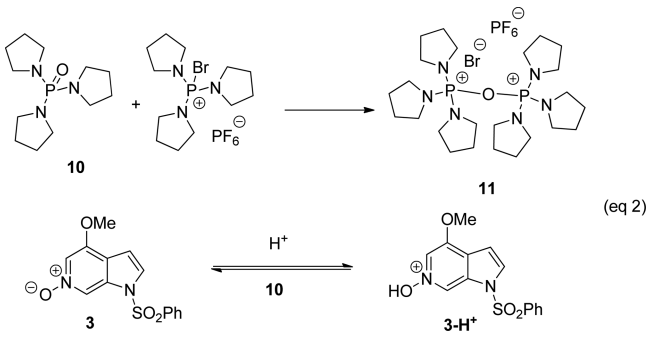
(BSA) was identified as the additive of choice. In the presence of 1 equiv of BSA, the reaction consistently furnished 85−90% solution yield of the brominated product **4** with >10:1 selectivity (entry 2, Table 5), representing a very significant improvement over the DIPEA-based process.

The bromination was monitored by NMR spectroscopy to gain insight into the reaction mechanism and the role of BSA. Since the reaction mixture is heterogeneous in toluene, the NMR studies were conducted in $CDCl_3$. In this solvent the reaction proceeded cleanly, but with lower selectivity (3:1). Reaction between equimolar amounts of **3** and PyBroP in the absence of additive resulted in reaction stalling. The NMR spectroscopy experiments suggested two possible causes for this observation. First, in the absence of an additive, the ^{1}H NMR resonances corresponding to *N*-oxide **3** shifted downfield as the reaction progressed. This observation can be attributed to the protonation of *N*-oxide **3** with the HPF_6 formed during the reaction,[21] which in turn could hamper the formation of intermediate **8**. Second, we observed the formation of a new phosphorus-containing product consistent with oxygen bridge dimer **11**.[22] Compound **11** was independently prepared by mixing PyBroP and tris(pyrrolidino)phosphine oxide **10**, one of the bromination byproducts, and was demonstrated not to be a competent brominating reagent under the reaction conditions (eq 2). Consequently, the formation of **11** is likely responsible

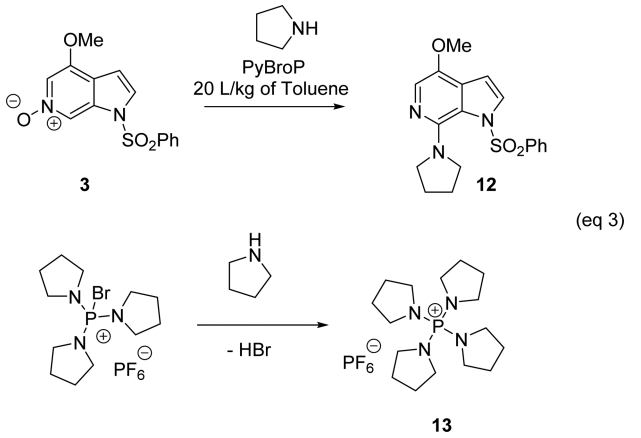


for the stalling observed in the absence of additives, which is consistent with byproduct inhibition. To assess the role of BSA in circumventing this competitive pathway, we combined equimolar amounts of bisphosphonium salt **11** and BSA and observed complete conversion to **10**. In an independent experiment, the addition of **10** to a solution of the protonated *N*-oxide **3** resulted in a shift of the equilibrium toward the unprotonated form (eq 2).[21b] Collectively, these data suggest that **10** is involved in scavenging the C-7 proton released during the reaction. BSA may either preclude or reverse the formation of **11** ensuring **10** and PyBroP are available to promote the desired reaction. Importantly, the addition of PyBroP to an equimolar mixture of **3** and **10**, in the absence or BSA, resulted in an increase in the reaction rate relative to the reaction with BSA. However, the reaction stalled at 55% conversion as PyBroP was consumed to form the bisphosphonium salt **11**.

When the bromination reaction was carried out in the presence of BSA in $CDCl_3$, we observed a phosphorus-containing byproduct that did not match the ^{31}P NMR spectrum of either **10** or **11**.[23] We reason that BSA is not solely acting as a desiccant but is also reducing the extent of the formation **11**. Further investigations on the scope and the mechanism of the PyBroP/BSA bromination of *N*-oxide are ongoing.

With the PyBroP/BSA conditions in hand, we focused our attention on the reaction mixing. The reaction begins as a thin solid suspension and gradually converts to a biphasic solution with a small volume of a heavy oil phase and a liquid phase. The analysis of each phase by NMR and HPLC confirmed minimal concentration of reactants present in the liquid phase (mostly toluene) suggesting that the reaction occurs in the oil phase.[24] We explored the effect of agitation to determine any potential issues that could be caused by inadequate dispersion of the oil phase in the toluene. We found no difference in rate between reactions in which the oil phase was fully settled compared to when the oil phase was fully dispersed.. These results provided assurance that differences of mixing upon reaction scale up and use of different equipment configurations would not have a negative impact on the reaction performance.

The quality of PyBroP plays an important role in the outcome of the bromination. During the course of development, we observed the formation of the pyrrolidine containing impurity **12** in the reaction mixture. The (tetrakis)pyrrolidinophosphonium salt **13**, a common impurity in PyBroP,[25] was independently synthesized and does not promote the formation of **12**, suggesting that free pyrrolidine is the likely culprit (eq 3).



The levels of **12** formed in the bromination reaction were particularly high (up to ∼10%) in reactions using improperly stored lots of PyBroP.[26] Although the impurity **12** could be effectively purged during the crystallization and isolation of **5**, its formation would result in a lower isolated yield. Therefore, an important factor to successfully executing this process was use of high quality PyBroP and proper storage of this reagent.

The optimized process based on the use of BSA as a key additive has been demonstrated in up to a 200 kg scale providing the bromination product **4** with similar selectivities to those observed during the laboratory development. Upon reaction completion, the process stream containing the brominated product **4** in toluene was carried forward into the benzenesulfonyl deprotection step.

Hydrolysis and Isolation. The initial conditions[1] employed IPA as a cosolvent and aqueous NaOH as the base resulting in the formation of high levels of isopropylbenzenesulfonate, a known genotoxic impurity (GTI).[27] To avoid its formation, we decided to evaluate a number of polar aprotic cosolvents. High conversions (>90%) were observed with dimethyl sulfoxide (DMSO), dimethylformamide (DMF), dimethylamide (DMA), and *N*-methyl-2-pyrrolidone (NMP), with the latter chosen for additional development. Under optimized conditions, NMP and aqueous NaOH were added to

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the toluene stream containing crude intermediate **4**, and the resulting solution was heated to 65−70 °C to give >99% conversion to **5**. We also developed a workup and hydrochloride salt crystallization that enabled the isolation of material with acceptable quality. This initial process allowed the delivery of enough material to support program requirements but had a number of issues that required additional attention: (a) multiple back extractions were needed to minimize material losses during the aqueous workup, (b) low potency of the isolated **5**-HCl was obtained due to the presence of residual inorganics and NMP, and (c) slow filtration was observed during isolation and formation of hard lumps during drying.

These challenges were mostly linked to the use of NMP as a cosolvent and were also expected to apply if using any other water miscible polar aprotic solvents. To minimize product loss during the aqueous workup and thereby eliminate the need for extensive back extractions, we explored the use of *tert*-amyl alcohol, which has partial water miscibility and high product solubility. In addition, the inherent GTI risk associated with the use of an alcohol in this reaction would not be a concern in the case of the tertiary alkylsulfonate.[28] Reaction mixtures containing variable amounts of *tert*-amyl alcohol afforded similar reaction rates to those observed with NMP as cosolvent (Table 6).

Table 6. Deprotection of 4 at 75 °C in the Presence of Mixtures of Toluene and *tert*-Amyl Alcohol

entry	% v/v *tert*-amyl alcohol in toluene	conversion (%) after 20 h at 75 °C
1	25	13.5
2	50	87.7
3	75	99.9

After optimization, the deprotection reaction was modified by conducting a partial solvent switch from toluene to *tert*-amyl alcohol (target ≥75% *tert*-amyl alcohol to achieve acceptable hydrolysis reaction rate), followed by addition of aqueous 5N NaOH and heating to 75 °C.

The use of *tert*-amyl alcohol also provided significant benefits to the workup and isolation. The product preferentially partitioned into the organic phase (>50:1 compared to 1:1 in the NMP process), thus eliminating the need for back extractions and reducing the product loss to the aqueous workup to 1−4% (compared to 6−11% in the NMP process). After the initial split of the basic aqueous phase, the resulting organic layer was sequentially washed with aqueous KH_2PO_4 and H_2O to remove pyrrolidine, other PyBroP related-impurities, and inorganic impurities. This new workup was instrumental for increasing the potency of the final isolated product.

Optimization of the crystallization conditions was informed by a solubility map of **5**-HCl within a range of water and HCl concentrations. By regression of the solubility data,[29] we found that the solubility of **5**-HCl is primarily impacted by the water concentration (Figure 2).

To minimize losses to the mother liquor, we conducted an azeotropic distillation to achieve water content of <1 wt % before executing the crystallization. This distillation also removed the remaining toluene and provided a consistent input composition into the crystallization.

The salt formation was carried out by controlled addition of aqueous HCl to a solution of the bromoazaindole **5** at 45 °C.

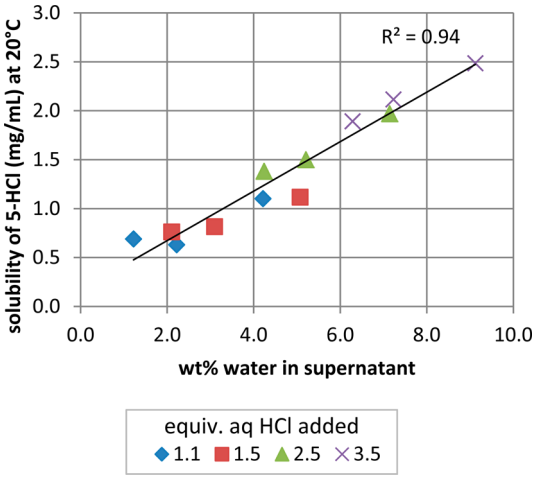

Figure 2. Solubility of **5**-HCl in mother liquors with varying water content and equivalents of HCl.

The resulting suspension of **5**-HCl was filtered and washed with *tert*-amyl alcohol. These modifications gave a low viscosity slurry that filtered and dried faster than the material obtained in the NMP process. Furthermore, the dry cake did not require delumping.[30]

Scale-up Summary. The optimized process, which includes the oxidation, bromination, hydrolysis, and salt formation steps, was demonstrated in up to 230 kg scale to provide overall isolated yields of 62−69% (>85% average yield per step) and consistent product purity of >99 area%. The *N*-oxide GTI impurities were controlled within the limits in all batches.[9]

Over the course of development, the gains in process understanding led to modifications of each operation which resulted in increased robustness and yields relative to the enabling process used to support initial material demands (Table 7).

Table 7. Comparison between Initial and Modified Processes for the Production of 5

	enabling process	optimized process
scale demonstrated (kg input per batch)	110 kg	230 kg
average isolated yield	49.6%	64.3%
average purity	97.7 area %	99.4 area %
average potency (wt % as HCl monohydrate)	93.6%	97.1%

CONCLUSION

We have developed a scalable synthesis of a key intermediate toward the preparation of BMS-663068. The route entailed oxidation of a 6-azaindole, bromination of the intermediate *N*-oxide, and final deprotection and isolation. Key accomplishments include: (a) improved safety by avoiding isolation of a highly energetic and mutagenic *N*-oxide; (b) reduced cost by using phthalic anhydride and aqueous H_2O_2 in the preparation of the *N*-oxide; (c) addressed yield and material balance variability during the oxidation by identifying the instability of the *N*-oxide, implementing a slow H_2O_2 addition and modifying the workup; (d) addressed reaction stalling in the bromination reaction and demonstrated that BSA can be used as an additive for optimal conversion, selectivity, and yield; (e)

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eliminated the GTI concerns related to isopropylsulfonate, need for iterative back extractions, and slow filtration of the hydrochloride salt by judicious choice of the hydrolysis cosolvent and fundamental understanding of the crystallization space. In summary, we have applied first-principles to improve each operation of the synthetic route to the key brominated azaindole **5**-HCl resulting in remarkable yield and quality improvements. The use of PyBroP/BSA as a brominating system may prove useful in the functionalization of other heterocyclic *N*-oxides.

EXPERIMENTAL SECTION

General Information. All reagents were used as received without further purification. The reaction progress and final product purity were monitored using HPLC using an Ascentis Express C18, 2.7 μm 4.6 × 150 mm column at 25 °C. Mobile phase A: 0.01 M NH_4OAc in H_2O:MeOH (80:20), mobile phase B: 0.01 NH_4OAc in H_2O−MeCN−MeOH (5:75:20), 1.0 mL/min. Gradient is shown in Table 8.

Table 8. Experimental Gradient

	mobile phase composition		
time (min)	% A	% B	gradient profile
0.0	100.0	0.0	initial
5.0	70.0	30.0	linear
20.0	55.0	45.0	linear
25.0	0.0	100.0	linear
30.0	0.0	100.0	hold

7-Bromo-4-methoxy-1*H*-pyrrolo[2,3-*c*]pyridine Hydrochloride Monohydrate (5-HCl). CH_2Cl_2 (3724 kg), **2** (200 kg, 1.0 equiv), and phthalic anhydride (134 kg, 1.3 equiv) were charged to an 8000 L glass lined vessel. The resulting mixture was heated to 35 °C. A 30% (w/w) aqueous solution of hydrogen peroxide (80.9 kg, 1.2 equiv) was added via pump over 2 h.[31] The resulting suspension was stirred at 35−37 °C for an additional 2 h, then sampled and analyzed by HPLC to determine the reaction progress. Once the oxidation reaction was deemed complete, the mixture was cooled to 10 °C. The reaction was quenched by controlled addition of a solution of sodium sulfite (88 kg) in water (1400 kg) such that the internal temperature remains below 20 °C. The typical addition time for a 200 kg batch is 2−4 h. The resulting biphasic mixture was stirred vigorously at 20 °C for 2 h to ensure complete reduction of any residual oxidant. A solution of K_3PO_4 (380 kg) in water (1400 kg) was then added to the quenched reaction mixture and the biphasic mixture stirred at 20 °C for 2 h. The top aqueous phase was discarded, and the product rich organic phase was washed with water (1400 kg). The bottom product rich organic phase was transferred to a clean 8000 L reactor.[32]

Toluene (1740 kg) was added, and the batch concentrated (≤0.25 MPa, internal $T \leq 30$ °C, jacket $T \leq 40$ °C), to a volume of 3000 L. A put and take distillation was then performed with toluene (1740 kg), and the batch was concentrated to a final batch volume of 3000 L. *N*,*O*-Bis(trimethylsilyl)acetamide (142 kg, 1.0 equiv) was added and the batch cooled to 10 °C. PyBroP (390 kg, 1.2 equiv) was added to the batch, and the resulting mixture was stirred for 15 h, then sampled and analyzed.[1] During this time the reaction mixture transforms changes from a thin solid suspension to a biphasic mixture composed of a heavy oil phase (bottom) and a clear colorless liquid phase (top).

After completion of the bromination reaction, *tert*-amyl alcohol (1620 kg) was added, and the mixture was concentrated to 3000 L (0.05 to 0.25 MPa, internal $T \leq 48$ °C). A second portion of *tert*-amyl alcohol (1620 kg) was added, and distillation to 3000 L was repeated. A solution of sodium hydroxide (200 kg) in water (1000 kg) was added to the reactor at such a rate that the internal temperature is maintained below 40 °C. The typical addition time for a 200 kg batch is 30−60 min. The resulting homogeneous mixture was then transferred to an 8000 L stainless steel vessel and heated to 75 °C for 10 h. The reaction mixture was cooled to 20 °C; the phases were allowed to split and were then separated. The aqueous layer was discarded. The top phase (product-rich) was sequentially washed with water (1000 L), a solution of K_2HPO_4 (100 kg) in water (1000 L), and water (1000 L).

The organic stream was transferred to an 8000 L glass lined vessel through a polish filter (1 μm), then concentrated (0.04−0.09 MPa, internal T 20−50 °C) to a final volume of 2000 L. *tert*-Amyl alcohol (1620 kg) was added, and the resulting solution was again concentrated under vacuum to 2000 L. The resulting mixture was heated to 35 °C, and then aqueous HCl (86 kg, 35 w/w %, 1.2 equiv) was added over 2 h. The resulting suspension was cooled to 20 °C over 1 h and then stirred for 2 h. The product was collected by centrifugation, washed twice with toluene (436 kg each), and dried at 50 °C at <0.1 MPa to afford the brominated azaindole **5** as an off-white solid, 124.8 kg (62.6% corrected yield).

M.p.: 160 °C (decomposition). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 12.66 (s, 1 H), 7.80 (m, 1 H), 7.69 (s, 1 H), 7.5−8.1 (s, *br*, 3 H), 6.74 (dd, J = 2.9, 1.9, 1 H), 3.98 (s, 3 H). ^{13}C NMR (125 MHz, DMSO-d_6) δ: 149.8, 133.7, 131.8, 126.8, 115.8, 114.0, 101.0, 56.8. HRMS [M + H; ESI-ORBITRAP] calc. for $C_8H_8BrN_2O$ (as free base): 226.9820; found: 226.9813.

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Notes

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(10) CH_2Cl_2 content (<1% v/v) and residual H_2O (KF < 100 ppm) were controlled in the toluene stream to ensure optimal performance of the bromination step. This reaction mixture showed an onset temperature of 110 °C and the T_{AD} reduced to 40 °C, thus allowing for a good safety margin under the process operating conditions. Toluene was chosen since it was the optimal solvent for the bromination step.

(11) HPLC analysis showed minimal differences between high and low yielding reactions which further complicated identification of the root cause. Quantitative mass analysis proved challenging due to the heterogeneous nature of the reaction. Biphenyl was employed as an internal standard for reproducible quantification by HPLC.

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(16) We have reported the bromination of heterocyclic *N*-oxides using Ts_2O/*n*-Bu_4Br: (e) Wengryniuk, S. E.; Weickgenannt, A.; Reiher, C.; Strotman, N. A.; Chen, K.; Eastgate, M. D.; Baran, P. S. *Org. Lett.* **2013**, *15*, 792−795 The application of this methodology to the bromination of compound **3** will be reported in due course..

(17) The reduced byproduct **2** is formed via a competitive mechanism. Control experiments showed that compound **4** does not undergo debromination under the reaction conditions. The addition of tetrabutylammonium bromide (TBABr) as an additive leads to larger amounts of **2**.

(18) We reasoned that the particle size effect on reaction performance is linked to the low solubility of K_3PO_4 in trifluorotoluene. The use of other solvents (i.e., CPME, MTBE, DCM, 1,2-DCE, THF, acetone, DMF, DMA, NMP) and other bases afforded lower yields and selectivites.

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(29) Since the process stream contains impurities that affect the product solubility, measuring the solubility in neat solvents was not informative; therefore, we employed mother liquors.

(30) The cake resistance was 4×10^{10} m/kg, which equates to a 7-fold increase in filtration rate over the toluene/NMP initial crystallization. For a leading reference of cake resistance: am Ende, D. J. *Chemical Engineering in the Pharmaceutical Industry*, John Wiley & Sons: Hoboken, NJ, 2011.

(31) The reaction was evaluated by calorimetry on RC1. It was found to be exothermic, with $\Delta H_{rxn} = -120$ kJ/mol, and $T_{ad} = +13$ °C. By ARSSt, no self-heating or self-pressurizing events observed up to 150 °C, including when Fe_2CO_3 was spiked into the reaction.

(32) The addition of PyBrop is not exothermic. The biphasic stream following PyBroP addition was evaluated for thermal hazards by Advanced Reactive Systems Screening Tool (ARSSt): 2.0 °C/min. Upon heating the mixture to 200 °C at 2.0 °C/min, an increase in the heating rate up to 2.0 °C/min over the background was observed with an onset of 110 °C. The heating rate was steady up to the test temperature and did not exhibit any second-order characteristics, which would be indicative of a potential runaway condition.

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