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Development of a Sequential Tetrahydropyran and Tertiary Butyl Deprotection: High-Throughput Experimentation, Mechanistic Analysis, and DOE Optimization

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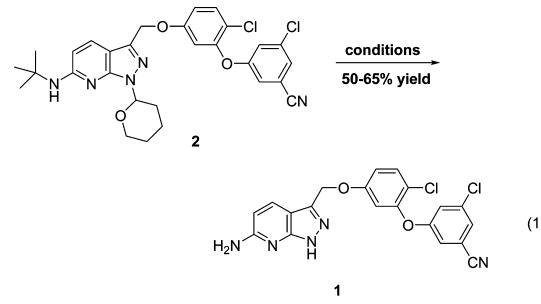
Abstract:

The synthesis of compound 1 by deprotection of the THP, *tert*-butyl protected amino-pyrazolopyridine (2), is described. The original conditions for this transformation were conducted in a one-pot procedure and necessitated the use of large quantities of either TsOH or benzenesulfonic acid (5 equiv) and trifluoroacetic acid (10−25 equiv) and produced 1 in moderate yield (50−65%). A series of high-throughput screens of Brønstead acids, Lewis acids, and solvents was rapidly performed with the goal of identifying improved efficiency and reaction yield. Through these screens, sulfuric acid was discovered to be a suitable replacement; however, yields of 1 were still unacceptable. A decoupling of the two deprotection steps revealed that the THP byproduct resulting from removal of the THP protecting group was problematic in the subsequent removal of the *tert*-butyl group. Consequently, a two-step deprotection protocol was developed which, in combination with design of experiment (DOE) optimization, improved the overall yield to ~86%.

Introduction

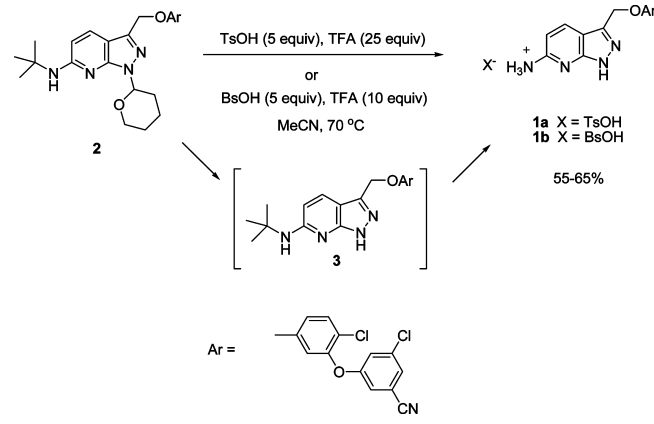
Reverse transcriptase inhibitors (NNRTI) have been shown to display a broad spectrum of activity against key HIV-1 RT mutations. While there are currently three NNRTIs on the market that have demonstrated clinical efficacy against HIV-1 RT mutations (efavirenz, nevirapine, and delavirdine),[1] treatment-related failure due to the emergence of clinical resistance remains a recurring issue. Therapies that have a broader spectrum of activity against mutant viruses and have a high genetic barrier to the selection of new resistant strains have resulted in the development of second-generation NNRTIs such as etravirine (TMC-125) which was recently approved by the FDA.[2] As part of a program to develop potent, orally active NNRTIs that possess an even broader spectrum of mutant activity, Merck has identified a novel class of second-generation NNRTIs from which compound **1** was brought forward for preclinical and clinical development.[3] During our work in the preparation of **1**, we found that deprotection of both the tetrahydropyranyl (THP) group and the *tert*-butyl group in the penultimate structure **2** proved difficult with yields for the one-pot procedure ranging from 50−65% (eq 1). In an effort to improve the overall efficiency of the final process with the primary goal of increased yield and purity, we reexamined the deprotection step in greater detail. In this paper, we document the development of the final optimized process leading to the formation of **1**.



Results and Discussion

The use of protecting groups is often a necessity in the preparation of advanced synthetic intermediates, and the preparation of **1** required both protection of the pyrazole nitrogen atom (THP protection) and the amino-pyridine nitrogen (*tert*-butyl).[4] While it was envisioned that removal of the THP group of **2** would be trivial, removal of the *tert*-butyl group from the amino-pyridine nitrogen would require more forcing conditions.[5] Fortunately, a recent report describing both the preparation and deprotection of *tert*-butyl-amino-pyridines appeared from these laboratories describing the use of TFA at 70 °C.[6] It was initially discovered that deprotection of **2** in the presence of dry TsOH (5 equiv) and TFA (25 equiv) in MeCN at 70 °C for 3 h afforded tosylate salt **1a** which crystallized from the crude reaction mixture and was isolated in 65% yield for the one-pot process (Scheme 1). Despite the modest yield and the simplicity of the process, key drawbacks with this

Scheme 1



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(1) Tarby, C. M. *Curr. Top. Med. Chem.* **2004**, *4*, 1045.
(2) http://www.tibotec.com/bgdisplay.jhtml?itemname=HIV_tmc125.
(3) Tucker, T.; Sisko, J.; Tynebor, R.; Williams, T.; Felock, P.; Flynn, J.; Lai, M.-T.; Liang, Y.; McGaughey, G.; Liu, M.; Miller, M.; Moyer, G.; Munshi, V.; Perlow-Poehnelt, R.; Prasad, S.; Reid, J.; Sanchez, R.; Torrent, M.; Vacca, J.; Wan, B.-L.; Yan, Y. *J. Med. Chem.* **2008**, *51*, 6503.

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process included the need to azeotropically dry the TsOH and the use of a large excess of TFA. It is important to note that TsOH or TFA alone did not provide **1**, and the use of either acid rapidly produced the des-THP intermediate **3** and failed to proceed further to **1**. Furthermore, the use of MeCN was also crucial for success as other solvents investigated resulted in either only the formation of **3** or led to the formation of other reaction byproducts. This chemistry was somewhat refined by the use of anhydrous benzenesulfonic acid (BSA), eliminating the azeotropic drying step required when TsOH was employed. In addition, the TFA charge was further optimized to 10 equiv. For example, treatment of **2** in MeCN with 5 equiv of BSA and 10 equiv of TFA and heating for 2 h at 70 °C resulted in the direct isolation of benzenesulfonate salt **1b** from the crude reaction mixture in comparable yield (65%). However, a route for long-term manufacture required further improvement. Unfortunately, all attempts to increase the yield of **1** using the chemistry outlined in Scheme 1 proved unsuccessful. We therefore used, as detailed below, high-throughput experimentation (HTE), coupled with DOE optimization, to help identify the optimal conditions for the conversion of **2** to **1**.

High-Throughput Acid/Co-Acid Screen. As our initial scouting experiments suggested that two acids were needed for the deprotection, we sought to examine a variety of Brønstead acids in the presence of either another Brønstead acid or a Lewis acid (Table 1).[7] We opted to perform a high-throughput screen

Table 1. **Initial high-throughput screen of solvent, acid, and co-acid[a]**

solvent	acid (7 and 15 equiv)	co-acid (2 equiv)
	First Screen	
acetonitrile	trifluoroacetic acid	benzenesulfonic acid
2-MeTHF	dichloroacetic acid	$MgBr_2$
	oxalic acid	$Al(iOPr_3)$
	chloroacetic acid	$ZnCl_2$
	trichloroacetic acid	BF_3
	phosphoric acid	
	Second Screen	
acetonitrile	oxalic acid	$MgBr_2$
acetic acid	malonic acid	LiBr
	succinic acid	$PhB(OH)_2$
	glutaric acid	benzenesulfonic acid
	adipic acid	
	phthalic acid	
	phosphoric acid	
	sulfuric acid	
	formic acid	
	citric acid	
	$PhB(OH)_2$	
	HCl (conc)	

[a] Conditions: 70 °C, 3 h.

in a 96-well microtitre plate format as this would offer the most efficient and material-sparing method to study a host of variables.[8] The Brønstead acids employed in our first screen had pK_a values approximately equal to or lower than that of trifluoroacetic acid, and the Lewis acids chosen were viewed as being economically viable for scale-up should they be successful. The initial screen was simply to assess the performance of these acids vs conversion to **1**.

Selected results from the first screen are shown in Table 2. Oxalic acid and phosphoric acid in the presence of either BSA

Table 2. **Co-acid, HPLC conversion to 1 (area %); selected results in acetonitrile from the solvent/acid screen detailed in Table *1*[a]**

entry	acid (7 equiv)	First Screen no co-acid	BSA (5 equiv)	$MgBr_2$ (2 equiv)
1	trifluoroacetic acid	2	81	73
2	oxalic acid	3	98	97
3	chloroacetic acid	1	80	33
4	phosphoric acid	2	80	91
		Second Screen		
entry	acid (7 equiv)	LiBr (2 equiv)	BSA (2 equiv)	$MgBr_2$ (2 equiv)
5	oxalic acid	100	93	100
6	malonic acid	12	83	96
7	succinic acid	1	50	69
8	sulfuric acid	100	100	100
9	phosphoric acid	75	61	75
10	HCl	94	82	94

[a] Complete results are in the Supporting Information.

or $MgBr_2$ co-acids (entries 2 and 4) produced **1** in comparable conversion to the original BSA/TFA conditions (Scheme 1). In the absence of the co-acids, negligible conversion occurred.

We were encouraged by the results from this first screen since both oxalic and phosphoric acids could serve as economically acceptable replacements for BSA and TFA. A second high-throughput screen was performed with the goal of elaborating upon the initial results and expanding the list of acids, including organic, mineral, and Lewis acids (Table 1, second screen).

Selected results from the second screen are highlighted in Table 2 (second screen). In general, oxalic acid (entry 5) in combination with BSA, $MgBr_2$, and LiBr was found to give the best conversion compared to the other organic acids we examined; however, very good reactivity was also observed with malonic acid with BSA and $MgBr_2$ (entry 6). In general, the stronger organic acids produced improved conversions as illustrated by a plot of pK_a against HPLC area percent conversion (Figure 1).[9,10] The outlier in this graph is cyanoacetic

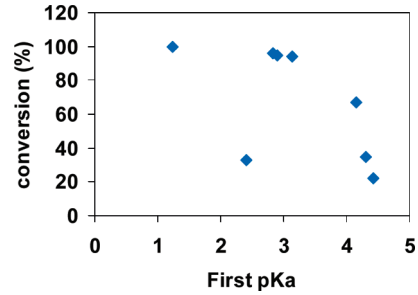


Figure 1. **Plot of pK_a (aqueous) vs HPLC area percent conversion for the reaction of 2 with organic acids and magnesium bromide in acetonitrile. Cyanoacetic acid, with a pK_a of 2.4 gave 33% conversion.**

acid where it is believed that the cyano functionality might interact with either the THP or *tert*-butyl byproduct. It is unclear why magnesium and lithium bromide have such an important effect on conversion. We propose that they can potentially serve as a source of HBr upon reaction with the organic acids (*vide*

infra), which, based upon our results with HCl, should function as a viable deprotection reagent. The bromide ion could also serve as a trap for the THP cation generated after deprotection. Alternatively, both magnesium and lithium might serve as a Lewis acid and activate the *tert*-butyl group toward elimination through coordination of the magnesium to both the *tert*-butylamino and the pyridine nitrogen atoms.

For the mineral acids, we were pleased to discover that sulfuric acid gave quantitative conversion of **2** to **1** in all cases. In fact, sulfuric acid exhibited this reactivity *regardless* of the identity of the co-acid. In contrast, both phosphoric acid and concentrated HCl exhibited a conversion dependence on the identity of the co-acid (Table 2, entries 9 and 10) with magnesium and lithium bromide producing better conversion than BSA. For sulfuric acid, we speculated that a co-acid was not necessary to influence conversion. We were therefore pleased to find that treatment of **2** with only sulfuric acid (7 equiv) in MeCN at 70 °C for one hour gave quantitative conversion to **1** albeit in only 65% HPLC assay yield.[11] This reaction was accompanied by the formation of black polymeric material similar to that observed in the original conditions. From our previous experience with the one-pot deprotection sequence employing BSA/TFA, it was known that the product **1b** was unstable to prolonged heating resulting in diminished yields (<65%). It should be noted that individual experiments with the oxalic acid/$MgBr_2$ conditions gave similar yields suggesting that additional acid screening would not likely be a means for improving the yield.

At this point in our optimization studies, the use of sulfuric acid for the deprotection was viewed as most promising in terms of cost and reaction simplicity, so we opted to focus attention on improving reaction yield via solvent screening (Table 3). A

Table 3. **Solvent screen employed to optimize reaction of 2 with sulfuric acid (3 equiv and 7 equiv)[a]**

solvents	
acetonitrile	dichloroethane
acetonitrile/water (90/10)	dimethoxyethane
acetonitrile/water (50/50)	2-ethoxyethanol
CPME/acetonitrile (50/50)	acetic acid
IPAc/acetonitrile (50/50)	DMSO/acetonitrile (50/50)
DMSO/acetonitrile (50/50)	sulfolane
ethanol/acetonitrile (50/50)	*N*-methylpyrrolidinone
DMF	ethanol/acetonitrile (50/50)
DMF/acetonitrile (50/50)	isopropyl acetate
toluene	acetonitrile/benzonitrile (90/10)
benzonitrile	acetonitrile (nBu_4NBr, 2 equiv)

[a] Conditions: 70 °C, 3 h. DMF = *N,N*-dimethylformamide, CPME = cyclopentylmethyl ether.

total of 22 different solvents were examined with both 3 and 7 equiv of sulfuric acid. All reaction mixtures contained 1,2-dichlorobenzene as an internal standard. The best results from this screen are shown in Table 4 and are reported in terms of

Table 4. **Selected results from the solvent screen[a]**

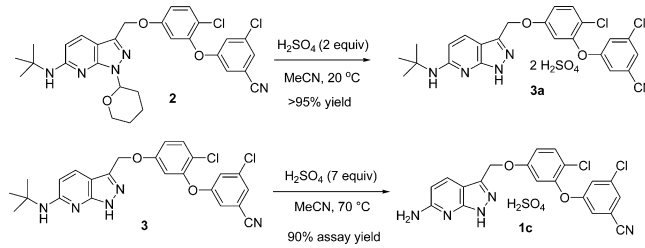
		% conversion to **1c** (rel yield[b])	
entry	solvent	H_2SO_4 (3 equiv)	H_2SO_4 (7 equiv)
1	acetonitrile	87 (2.1)	100 (1.4)
2	acetonitrile/water (90/10)	25 (0.7)	98 (3)
3	CPME/acetonitrile (50/50)	54 (1.3)	100 (2.6)
4	DMF/acetonitrile (50/50)	45 (1.4)	99 (3)
5	DMF	1 (0)	3 (0.1)
6	dimethoxyethane	87 (1.8)	100 (2)

[a] Complete results can be found in the Supporting Information. [b] Relative yield, defined as "area counts of product/area counts 1,2-dichlorobenzene".

conversion and relative yield against the internal standard. In general, 7 equiv of sulfuric acid gave greater conversions and higher relative yields than the reactions performed with 3 equiv. Acetonitrile was the best solvent in terms of conversion; however, we were pleased to find that the addition of co-solvents *improved the reaction yield* as well. For example, entries 2 (acetonitrile/water, 90/10) and 4 (acetonitrile/DMF, 50/50) had an improved relative yield versus acetonitrile (entry 1). Presumably, the addition of either water or DMF aids in the capture of the *tert*-butyl cation. When water was utilized, both *tert*-butylacetamide and ammonium sulfate were observed in the crude reaction mixture. Scaling up the best conditions from entries 2 and 4 (Table 4) to a 100 mg scale gave **1** in 70−75% yield with concomitant formation of black polymeric material. While this is a 5−10% improvement in yield over that observed in acetonitrile, we were not satisfied with this as a final solution and therefore shifted our attention toward developing a better mechanistic understanding of the overall deprotection.

Mechanistic Reaction Analysis. We believed that the individual analysis of the two deprotection steps would allow us to identify what contribution each step was making to the overall yield (Scheme 2). It was known from our screening

Scheme 2

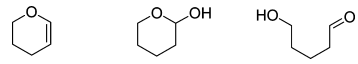


results that rapid removal of the THP group in **2** occurred at room temperature upon the addition of sulfuric acid. When the THP deprotection of **2** was performed at room temperature,

(4) The preparation of **2** will be the focus of a future publication.
(5) De Kimpe, N.; Sulmon, P.; Brunet, P. *J. Org. Chem.* **1990**, *55*, 5777.
(6) Yin, J.; Xiang, B.; Huffman, M. A.; Raab, C. E.; Davies, I. W. *J. Org. Chem.* **2007**, *72*, 4554.
(7) Experimental details of all the screens can be found in the Experimental Section.
(8) (a) Maligres, P. E.; Krska, S. W.; Humphrey, G. R. *Org. Lett.* **2004**, *6*, 3147. (b) Shultz, C. S.; Dreher, S. D.; Ikemoto, N.; Williams, J. M.; Grabowski, E. J. J.; Krska, S. W.; Sun, Y.; Dormer, P. G.; DiMichele, L. *Org. Lett.* **2005**, *7*, 3405. (c) Tellers, D. M.; Bio, M.; Song, Z. J.; McWilliams, J. C.; Sun, Y. *Tetrahedron: Asymmetry* **2006**, *17*, 550. (d) Tellers, D. M.; McWilliams, J. C.; Humphrey, G.; Journet, M.; DiMichele, L.; Hinksmon, J.; McKeown, A. E.; Rosner, T.; Sun, Y.; Tillyer, R. D. *J. Am. Chem. Soc.* **2006**, *128*, 17063.
(9) Bordwell, F. G. *Acc. Chem. Res.* **1988**, *21*, 456.
(10) (Absorbance Product/(Absorbance Product + Absorbance Starting Material)) × 100; absorbance is measured at 215 nm.

intermediate **3** was formed in >95% yield with concomitant formation of black polymeric material. The des-THP intermediate **3** was isolated by chromatography from this reaction mixture and subjected to a series of *tert*-butyl deprotection conditions. For example, when **3** was allowed to react with 7 equiv of conc H_2SO_4 in MeCN at 70 °C, the HPLC assay yield of **1c** was 90%! When **1c** was resubjected to the same reaction conditions, no detectable level of decomposition was observed after 2 h at 70 °C, and HPLC assay of **1c** was 97%. We had originally suspected that deprotection of the *tert*-butyl group in **3** was the problematic step. These results demonstrate that the *tert*-butyl deprotection was inherently a high-yielding reaction.

At this point, it was evident that the source of the low yield could be attributed to the potential byproduct associated with THP removal (Figure 2). Efforts were then focused on

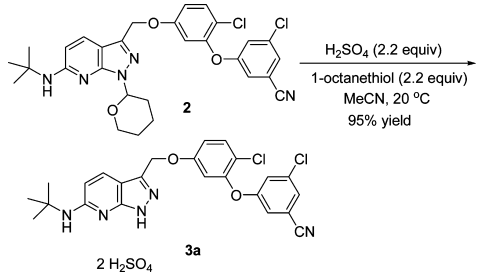


4 5 6

Figure 2. **Potential THP byproducts in the absence of trapping agents.**

completely removing these byproducts (i.e., including compounds **4**−**6**) prior to the *tert*-butyl group deprotection. After examination of a variety of trapping agents to sequester the THP byproduct and allow for the direct isolation of **3a** from the crude reaction mixture, the optimal conditions were discovered (Scheme 3). Treatment of **2** in MeCN with 2.2 equiv of conc

Scheme 3



H_2SO_4 in the presence of 2.2 equiv of 1-octanethiol resulted in the quantitative formation of des-THP intermediate **3a** within 10 min. The use of 1-octane thiol was crucial for obtaining crystalline **3a** and eliminating the formation of black polymeric byproduct associated with the THP removal.[12] During the course of the reaction, **3a** began to crystallize from the reaction mixture. After dilution with MTBE and then heptane to maximize the recovery, compound **3a** was isolated as bis-sulfate salt in 95% yield (98−99 LCAP) as a white to off-white crystalline solid. These conditions completely removed THP residues from the isolated product. A one-pot procedure for the conversion of **2** to **1c** employing octanethiol was also examined; however, the yield was ∼75% which was approximately 10% lower than a two-step process. The lower yield was attributed to the fact that the THP−octanethiol adduct may decompose at the elevated temperatures required for *tert*-butyl deprotection. The decomposition byproduct could then interfere with the *tert*-butyl cleavage as was observed under the original conditions. The two-step process was optimal since it effectively removed all THP residues via crystallization of **3a**, thereby removing any chance for deleterious side reactions in the subsequent step.

Design of Experiment (DOE) Optimization and Final Processing Conditions. Having optimized the THP deprotection to an acceptable yield, we then shifted our attention to optimizing the cleavage of the *tert*-butyl group. The final deprotection was initially screened with a few different concentrations of water, acid, and temperature, and variable yields of 80−94% were obtained. These scouting experiments suggested that water, sulfuric acid, temperature, and time were potentially important variables influencing the yield. We opted to perform a DOE optimization[13] on this step with the goal of quantitatively mapping these reaction parameters in terms of reaction robustness and identifying the best reaction conditions for scale-up.

We routinely employ DOE to compliment our HTE results. Whereas HTE is a powerful tool for identifying ideal *discreet* variables (e.g., solvent, acid, catalyst), DOE provides the optimal settings for the related *continuous* variables. The continuous variables chosen for this study and their settings are shown in Table 5.

Table 5. **Continuous variables (factors) for DOE study in acetonitrile**

factor (units)	range studied
term A. water/vol % in CH_3CN	0–10
term B. temperature/°C	55–75
term C. reaction time/h	2–8
term D. sulfuric acid charge/equiv	3–15

A 2^4 full factorial screening design with three replicate center points, to detect curvature in the design space, was selected for a total of 19 reactions. This design allowed for the interaction terms to be unaliased with each other. The reactions were performed in parallel on a 150 mmol scale. Analysis of the data[14] revealed that the most relevant factor influencing the yield was the interdependence of water content and sulfuric acid charge (AD term, Table 5). As shown in Figure 3, based on a linear analysis, at high water content (10 vol %), more sulfuric acid (15 equiv) is desirable to maximize the yield, but at *low* water content, less sulfuric acid gives better assay yields. This suggests that the molarity of the acid plays a role in the reaction. But of the two scenarios, the high water charge/high sulfuric acid charge combination was predicted to provide a better yield than the low water/low acid combination. This is consistent with the determination that the second most relevant factor is water content, in which more water uniformly gives higher yields, regardless of the sulfuric acid charge. It is notable that significant curvature (nonlinearity) was observed in the design space, as evidenced by the fact that the highest yields of all were the three replicate reactions run at the midpoint of the ranges (Figure

(11) The term "assay yield" refers to a nonisolated solution yield of product as determined by comparison of product UV absorbance with that of pure, authentic product standard using HPLC analysis.

(12) Although the deprotection in the absence of 1-octanethiol gave **3a** in high assay yield, isolation of **3a** in acceptable purity was difficult.

(13) For a leading reference on DOE concepts, see: Carlson, R.; Carlson, J. E. *Design and Optimization in Organic Synthesis*; Amsterdam: Elsevier, 2005.

(14) DOE analyses were performed using *Design Expert v 7.1.3* Stat Ease, Inc.: 2021 East Hennepin Ave., Suite 480, Minneapolis, MN 55413, U.S.A.

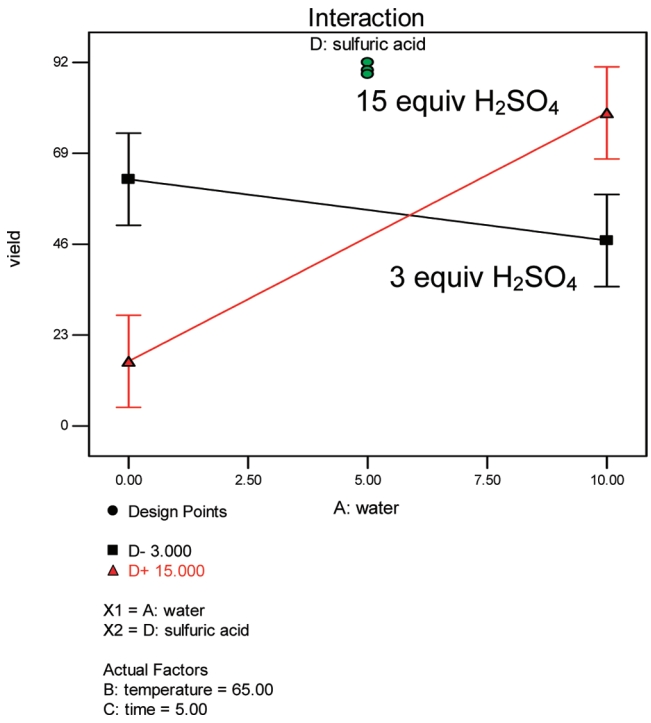


Figure 3. **Graph describing the interaction of factors A and D.**

3). This indicates that a linear response is not fully reflective of the true nature of response surface. This is common in screening designs which are meant to identify the relevant factors and their preferred qualitative settings (High or Low) and can only identify curvature but not describe it precisely.

The reaction time (factor C, Table 5) had no bearing on the yield, so the lower value of 3 h was selected for future experiments. Similar to the water content, the ideal temperature was dependent on the sulfuric acid charge with higher yields

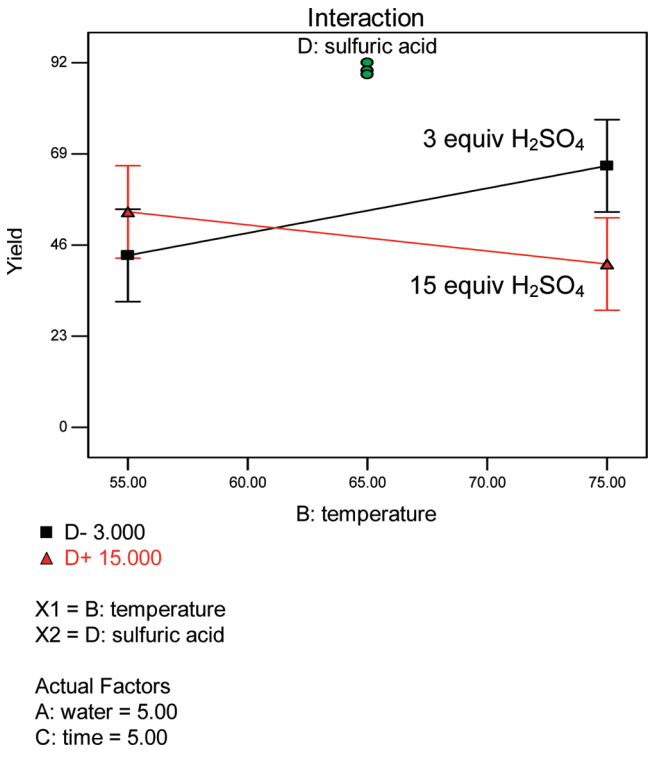


Figure 4. **DOE graph describing the temperature/acid charge interaction.**

observed at the higher temperature setting (75 °C) with a low acid charge (3 equiv) than at the lower temperature (55 °C) with a low acid charge (3 equiv), but again curvature was observed in the design space as the best yields were observed at the midpoint settings (65 °C/5 equiv water) (Figure 4).

In order to more fully elucidate the nature of the design space and map the curvature, a second study, employing a response surface model (RSM) was performed to compliment the information obtained in the initial DOE design. We used a face-centered central composite design (CCD) in which only the water content and sulfuric acid charge were investigated based on the results of the earlier design. The time (3 h) and temperature (65 °C) settings were held constant. The ranges for the two remaining factors were narrowed (water: 2−7 vol %; acid: 5−9 equiv) to accommodate both the region of interest from the screening design and practical processing requirements with respect to impurity generation (related to acid charge) and impurity rejection (related to water charge); this led to 11 reactions for which both assay yield and area % conversion were the measured responses. Analysis of the conversion response revealed the model contained no relevant terms therefore indicating that the conversion was robust over the entire design space and uniformly high (>95 A%). *The assay yield response indicated only the water charge was relevant, whereas the acid charge had little impact* (Figure 5). The model contained only the linear term for the water charge, indicating a linear response throughout the design space. On the basis of these data coupled with our observation that at low water charges (<1 vol %) the reaction yield began to diminish, we opted to use a water charge of 4 vol %. Despite the higher potential reaction yield at 2 vol % water (Figure 5), we believe

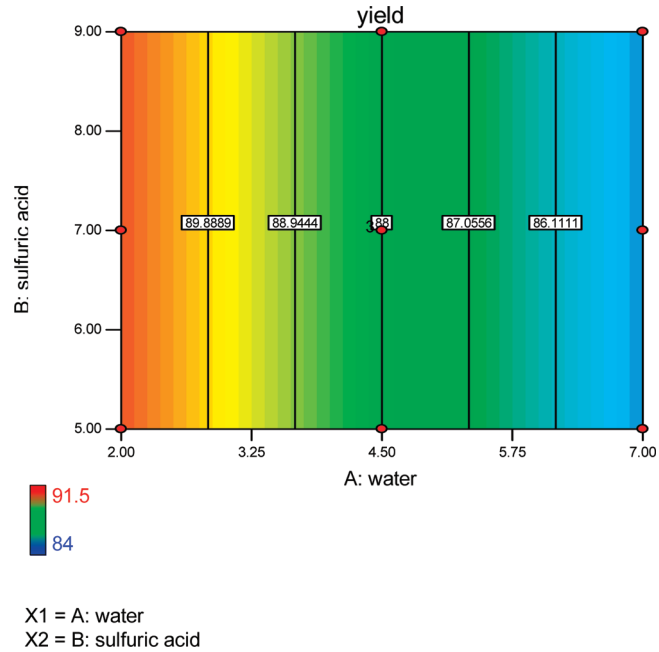


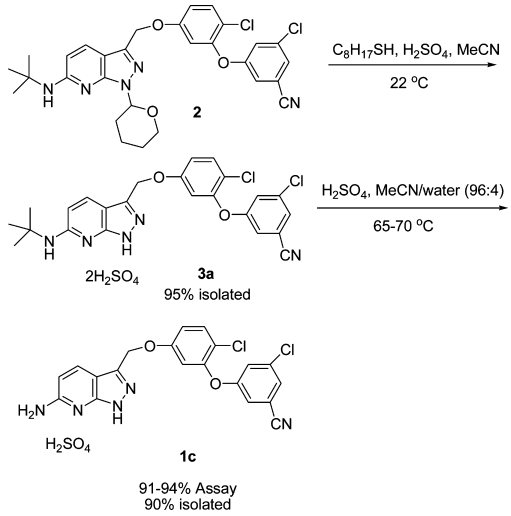
Figure 5. **Contour plot: effect of water and acid levels on yield.**

that higher water charge of 4% was a more robust processing point for our larger-scale processing and thus offset any potential yield gains offered by the lower water charge. To elaborate further, our data reveal a sharp drop in yield below 2 vol % water charge, and

we therefore opted to run at the higher water charge to minimize potential yield loss due to an incorrect water charge.

A successful scale-up of our optimized process was performed on isolated **3a** on a 50 g scale using 7 equiv of sulfuric acid and 4 vol % water at 65 °C for 2 h. During the course of the reaction, monosulfate salt **1c** began to crystallize from the crude reaction mixture. Assay yield for the *tert*-butyl removal was 92%, and after cooling and filtration, the monosulfate salt **1c** was isolated in 90% yield. Analysis of the crude reaction mixture by both NMR and HPLC did not reveal any hydrolysis of the nitrile of **1c**; however, hydrolysis of MeCN was observed. While not rigorously investigated, the formation of both acetic acid and *tert*-butylacetamide were observed. In addition, off-gassing of isobutylene was not detected, and it was believed that the water present in the reaction mixture was effectively trapping the *tert*-butyl cation. The final optimal conditions for the synthesis of **1c** from **2** are illustrated in Scheme 4.

Scheme 4. **Final process for the preparation of 1c**



Summary

We have described an improved procedure for the preparation of **1** from THP, *tert*-butyl protected amino-pyrazolepyridine **2**. We believe the increase in yield (more than 20% higher than the original yield), impurity profile, and robustness warrant the additional isolation step. The multifaceted approach involving high-throughput reaction screening, mechanistic analysis, and DOE optimization were essential to the development of this new process. The high-throughput screen allowed us to rapidly identify a new acid (H_2SO_4) for the deprotection step using a minimal amount of material: 1.2 g of **2**, 236 reactions, 3 days total for reaction setup and analysis. Greater understanding of the individual deprotection steps with sulfuric acid allowed us to make the observation that residues from the THP deprotection were solely responsible for the low yield in the one-pot procedure. Finally, DOE allowed us to define, better understand, and optimize the factors that were important to reaction yield and robustness.

Experimental Section

Reaction mixtures and products were analyzed by reverse phase HPLC on a Hewlett-Packard 1100 instrument using a 4.6 mm × 50 mm Zorbax Eclipse Plus C18 column. Solvent compositions consisted of 0.1% H_3PO_4 and acetonitrile with a flow rate of 1.5 mL/min.

Preparation of 3-{5-(6-*tert*-Butyl-amino-1H-pyrazolo[3,4-*b*]pyridine-3-ylmethoxy)-2-chloro-phenoxy}-5-chloro-benzonitrile Bis-sulfate (3a). A 1 L, three-neck, round-bottom flask equipped with a mechanical stirrer and thermocouple was charged with **2** (35.9 g, 63.4 mmol) in MeCN (100 mL) followed by addition of octanethiol (20.4 g, 139 mmol) in one portion. The reaction mixture was cooled to 15 °C, and concd sulfuric acid (7.4 mL, 140 mmol) was added dropwise over 30 min while maintaining the internal temperature <25 °C. The resulting homogeneous solution was stirred at room temperature for 30 min during which time **3a** began to crystallize from the crude reaction mixture. The resulting slurry was stirred at room temperature for 30 min, and MTBE (130 mL) was added dropwise over 45 min. The resulting slurry was stirred at room temperature for an additional 30 min, and heptane (65 mL) was added dropwise over 45 min; the slurry stirred for 3 h and was filtered. The wet cake was washed with MTBE (125 mL) and dried under vacuum/N_2 sweep for 8 h to give 40.85 g (95%) of **3a** as a white solid: mp 140 °C (DSC); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 1.25 (s, 9H), 4.67 (s, 2H), 6.08 (d, 1H, J = 9.4 Hz), 6.17 (d, 1H, J = 2.8 Hz), 6.27 (dd, 1H, J = 8.9 and 2.8 Hz), 6.32 (m, 1H), 6.36 (m, 1H), 6.69 (m, 2H), 7.44 (d, 1H, J = 9.4 Hz); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 26.5, 52.7, 60.7, 105.5, 108.6, 113.0, 113.7, 115.7, 117.4, 120.5, 125.2, 130.6, 135.3, 137.1, 144.9, 149.7, 152.4, 157.4, 157.6. Anal. Calcd For $C_{24}H_{25}Cl_2N_5O_{10}S_2$: C, 42.48, H, 3.71; N, 10.32. Found: C, 42.06; H, 3.66; N, 10.21.

Preparation of 3-{5-(6-Amino-1H-pyrazolo[3,4-*b*]pyridine-3-ylmethoxy)-2-chloro-phenoxy}-5-chloro-benzonitrile Sulfate (1c). To a 1 L round-bottom flask equipped with a mechanical stirrer, thermocouple, and reflux condenser were added **3a** (54.0 g, 79 mmol) and a 96:4 mixture of MeCN/water (350 mL, v/v). To the solution was added conc sulfuric acid (4.23 mL, 556 mmol), and the reaction mixture was heated to 70 °C for 2 h during which point the product began to crystallize from the crude reaction mixture. The slurry was cooled to room temperature and diluted with 190 mL of water. The slurry was stirred for 3 h and filtered. The wet cake was washed with 2:1 MeCN/water (150 mL, 2×) and dried under vacuum/N_2 sweep for 12 h to give 38.2 g (92%) of **1c** as a white solid: mp 225 °C (DSC); ^{1}H NMR (DMSO-d_6, 400 MHz) δ 5.45 (s, 2H), 6.64 (d, 1H, J = 9.2 Hz), 7.07 (m, 2H), 7.37 (dd, 1H, J = 2.3 and 1.2 Hz), 7.47 (dd, 1H, J = 2.3 and 1.2 Hz), 7.59 (m, 1H), 7.81 (s, 1H), 8.27 (d, 1H, J = 9.2 Hz); ^{13} NMR (DMSO-d_6, 100 MHz) δ 61.5, 106.7, 109.2, 109.9, 114.5, 114.6, 117.4, 117.7, 119.7, 122.3, 127.2, 131.9, 135.8, 136.9, 137.7, 145.8, 150.6, 156.1, 158.2, 158.4. Anal. Calcd For $C_{20}H_{15}Cl_2N_5O_6S_2$: C, 45.81; H, 2.88; N, 13.36. Found: C, 45.97; H, 2.98; N, 13.33.

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Supporting Information Available

A complete listing of DOE data, HTE screening protocol, original procedure for preparation of **1b** from **2**, and screening results.This material is available free of charge via the Internet at http://pubs.acs.org.

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