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Article

Development of a Scalable Electrophilic Amination Protocol for the Multi-kg Production of 5-Methyl-2-pyridinesulfonamide: A Regulatory Starting Material of Endothelin Receptor Antagonist Clazosentan

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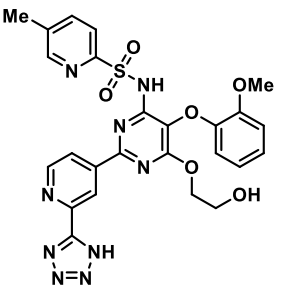
ABSTRACT: 5-Methyl-2-pyridinesulfonamide is a regulatory starting material of endothelin receptor antagonist clazosentan. The original route to the key sulfonamide relied on the textbook conversion of the corresponding thiophenol to the intermediate sulfonyl chloride followed by its quenching with aqueous ammonia. However, this route suffered from a wide range of issues such as a low overall yield (29%), challenging aqueous workups and isolations, and the formation of a genotoxic benzyl chloride impurity. Therefore, we developed a conceptually novel production route for 5-methyl-2-pyridinesulfonamide. The new process relied on selectively oxidizing the thiophenol to the intermediate sulfinate salt followed by an electrophilic amination of the nucleophilic sulfinate sulfur-atom with hydroxylamine-*O*-sulfonic acid (HOSA). This oxidation/electrophilic amination sequence worked as a "one-pot" procedure by simply adding HOSA to the reaction mixture after complete oxidation of the thiophenol with 70% aq. *t*-BuOOH. The process was extensively optimized with regard to the oxidation step, increasing the stability of HOSA in the reaction mixture, and the final isolation of 5-methyl-2-pyridinesulfonamide. The new process was performed on a 22 kg scale, delivering the desired product as a white solid in 69% overall yield and excellent purity (>99.9% a/a).

KEYWORDS: *pyridine, oxidation, amination, HOSA, sulfonamide*

INTRODUCTION

Aneurysmal subarachnoid hemorrhage (aSAH) is a sudden, life-threatening bleeding on the surface of the brain.[1] Symptoms of aSAH include a severe headache, confusion, and numbness in the body, among other warning signs. Patients with an aSAH will undergo surgery to stop the bleeding and prevent fatal re-bleeding. Between a few days and two weeks into their recovery, about a third of patients with aSAH experience a worsening of their neurological condition due to delayed cerebral vasospasm, a constriction, or tightening, of arteries in the brain.[2] Cerebral vasospasm restricts blood flow to the brain and may subsequently lead to the death of blood-starved brain tissue, a consequence known medically as cerebral infarction and accompanied by poor long-term outcomes. Currently, an invasive approach is used to treat cerebral vasospasm. This is associated with medical risks and often requires repeated procedures. Recently, clazosentan[3] (Figure 1) was evaluated in placebo-controlled, randomized, double-blind studies in adult Japanese patients post-aSAH treated by endovascular coiling or microsurgical clipping. Clazosentan was shown to reduce the occurrence of cerebral vasospasm-related morbidity and all-cause mortality within 6 weeks post-aSAH with statistical significance ($p < 0.01$ for both studies).[4] Subsequently, clazosentan was approved by the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) for the prevention of cerebral vasospasm, vaso-spasm-related cerebral infarction, and cerebral ischemic symptoms after aSAH.



clazosentan

Figure 1. Structure of clazosentan.

The synthesis of clazosentan has been previously disclosed and will not be discussed in this manuscript.[5] 5-Methyl-2-pyridinesulfonamide (**1**) is a regulatory starting material in the synthesis of clazosentan. Historically, **1** was commercially

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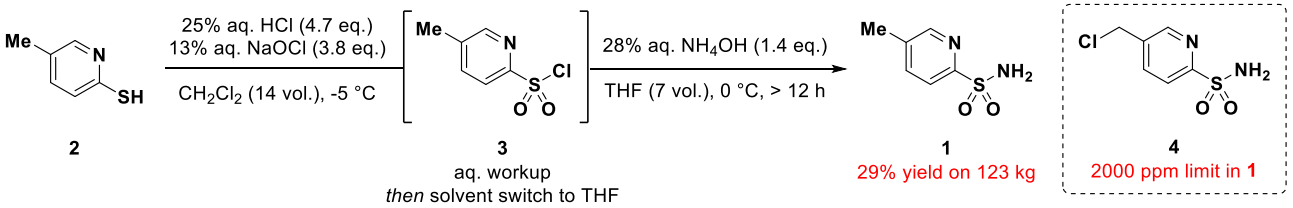
Scheme 1. Original Route to 1



available (CAS: 65938-77-4) on kg scale from a specific supplier. However, at one point, **1** could not be sourced anymore from this supplier and a new route needed to be rapidly developed to secure the supply of **1** for all clinical and commercial batches. A literature procedure[6] was adopted on scale by synthesizing **1** in a telescoped 2-step procedure from 5-methylpyridine-2-thiol (**2**) via the intermediacy of sulfonyl chloride **3** (Scheme 1).

While several multi-kg batches of **1** were successfully produced within specification using this classical sulfonyl chloride chemistry, the process was far from ideal. The most clamoring issues are summarized below:

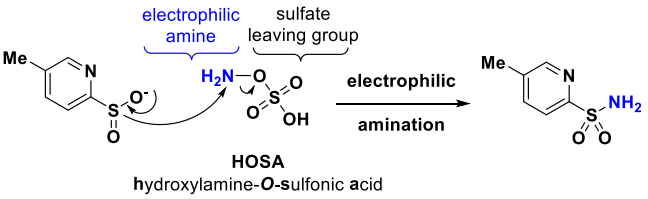
(a) a low isolated yield of **1** of only 29% on 123 kg scale (prior to rework, vide infra),
(b) the use of undesirable CH_2Cl_2 as reaction and extraction solvent and formation of Cl_2-gas in the oxidation step,
(c) two highly exothermic additions (NaOCl and aq. NH_4OH) that required extremely slow additions on scale (up to 24 h dosage time),
(d) stability issues of the intermediate sulfonyl chloride, which necessitated the solvent switch from CH_2Cl_2 to THF to be performed at IT ≤ 25 °C,
(e) difficult phase splits (THF/EtOAc and H_2O) during the isolation of **1**,
(f) heavy crust formation during the solvent switch of the organic layer to TBME to crystallize **1**, and, most importantly,
(g) high variability in the purity and color of the isolated product **1**, which necessitated several batches to be reworked in order to be within specifications.

Out of the identified impurities in **1**, 5-(chloromethyl)-pyridine-2-sulfonamide (**4**) was the most problematic one as it was identified as a genotoxic impurity.[7] As **4** needed to be strictly controlled below 2000 ppm at the stage of **1**, certain batches of **1** needed to be reworked to pass specifications (also for color), further lowering the overall isolated yield. As benzyl chloride **4** clearly originated from the use of NaOCl/HCl, we wanted to explore the possibility to synthesize **1** without the use of chlorine-based oxidants, with the ultimate goal of developing a robust, scalable process that does not suffer from any of the shortcomings listed above.

■ ROUTE SCOUTING AND DEVELOPMENT

As the formation of benzyl chloride impurity **4** and the highly unstable nature of **3** were two major issues, we wanted to develop a novel route that completely avoided the formation of an intermediate sulfonyl chloride. To this end, we were inspired by a seminal publication of Graham and Scholz on the electrophilic amination[8] of isolated sulfinate salts with hydroxylamine-*O*-sulfonic acid (HOSA) (Scheme 2).[9,10] HOSA is an inexpensive bulk chemical,[11] which can be produced by reacting hydroxylamine with oleum/sulfuric acid

Scheme 2. Electrophilic Amination of Sulfinates with HOSA



or with chlorosulfonic acid/sulfuric acid.[12] While there are a handful of reports on the application of the electrophilic amination protocol by Graham and Scholz, the sulfinate salts were normally generated in situ from an organometallic precursor (e.g., Ar−Li or Ar-B$(OH)_2$) and SO_2-gas or solid SO_2-surrogate.[13] However, these approaches were not attractive to us given the known, highly unstable nature of 2-pyridyl organometallic reagents.[14] Therefore, we hoped to prepare the sulfinate salt in situ from thiophenol **2** and an inexpensive, chlorine-free oxidant such as aqueous H_2O_2 or *t*-BuOOH and then directly treat the sulfinate with HOSA to give **1**. This would result in an elegant, vastly improved process for **1** without the intermediacy of sulfonyl chloride **3** or the possibility of generating benzyl chloride impurity **4**. To the best of our knowledge, such an in situ oxidation/electrophilic amination process has never been reported.

We started our optimization screenings with the partial oxidation of thiophenol **2** to sodium sulfinate **5-Na** by using 35% aq. H_2O_2 (2.0 equiv) and aq. NaOH in EtOH (Table 1). The reaction of aq. H_2O_2 with a basic solution of **2** in EtOH was clean and nearly dose-controlled at room temperature (RT) or 0 °C. However, varying amounts of over-oxidation to the sodium sulfonate **6-Na** were observed (Entries 1−4). The best conditions out of these early screenings were the combination of 1 M aq. NaOH (1.3 equiv) in EtOH and dosing of H_2O_2 (2.0 equiv) at 0 °C, leading to a ratio of **5**:**6** of 88:12 (Entry 1). Increasing the base concentration (Entries 2−4) led to an increased content of sulfonic acid **6**, while in the absence of the base (Entry 5) only the formation of the disulfide of **2** was observed. We speculated that a slightly bulkier oxidant might be able to reduce the sulfonic acid content even further. Indeed, when 70% aq. *t*-BuOOH (2.0 equiv) was used as the oxidant (Entries 6−9), the content of over-oxidation could be further limited to only 7−8% a/a by high-performance liquid chromatography (HPLC) using *t*-BuOH or EtOH as reaction solvents (Entries 8−9).[15]

With the optimal conditions in hand (Entry 9), we explored the conversion of the in situ generated sodium sulfinate salt **5-Na** into sulfonamide **1**. Simple addition of solid HOSA (1.5 equiv) to the reaction mixture at 0 °C followed by warming to RT led to a clean conversion of sulfinate **5-Na** into **1**. However, the conversion was slow and stalled at around 50%. Slight heating to IT = 45−50 °C after HOSA addition helped to increase the reaction rate and >95% conversion of **5-Na** was

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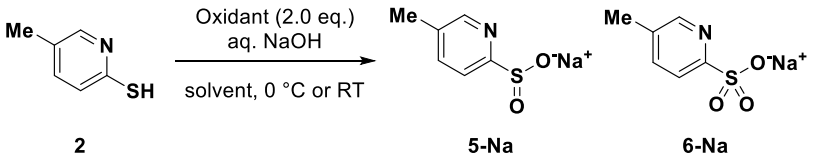
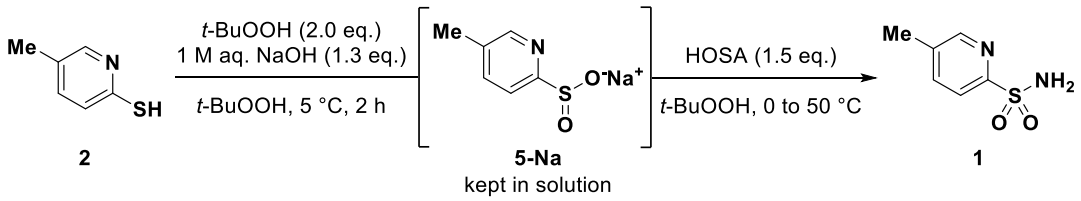
Table 1. Oxidation Screening of 2[a]



2 5-Na 6-Na

entry	oxidant[b] (2.0 equiv)	base (1.3 equiv)	solvent (5 vol)	temp	ratio 5-Na:6-Na[c]
1	H_2O_2	1 M aq. NaOH	EtOH	RT	85:15
2	H_2O_2	1 M aq. NaOH	EtOH	0 °C	88:12
3	H_2O_2	2 M aq. NaOH	EtOH	RT	70:30
4	H_2O_2	10.8 M aq. NaOH	EtOH	RT	65:35
5	H_2O_2		EtOH	RT	-[d]
6	*t*-BuOOH	1 M aq. NaOH	EtOH	RT	91:9
7	*t*-BuOOH	1 M aq. NaOH	*t*-BuOH	RT	92:8
8	*t*-BuOOH	1 M aq. NaOH	EtOH	0 °C	92:8
9	*t*-BuOOH	1 M aq. NaOH	*t*-BuOH	0 °C	93:7

[a]Conditions: **2** (1.0 g, 8.0 mmol, 1.0 equiv) and aq. NaOH (10.4 mmol, 1.3 equiv) in solvent (5 mL, 5 vol) at 0 °C or RT, *then* dosing of oxidant (16 mmol, 2.0 equiv) over 15 min. [b]H_2O_2 corresponds to 35% aq. H_2O_2 solution; *t*-BuOOH corresponds to 70% aq. *t*-BuOOH solution; ET = heating block. [c]Ratio of **5-Na** to **6-Na** was determined by in-process control (IPC) using HPLC at 265 nm, 1 h after complete dosing of the oxidant. [d]In the absence of a base, clean formation of the disulfide of **2** was observed.



2 5-Na 1

kept in solution

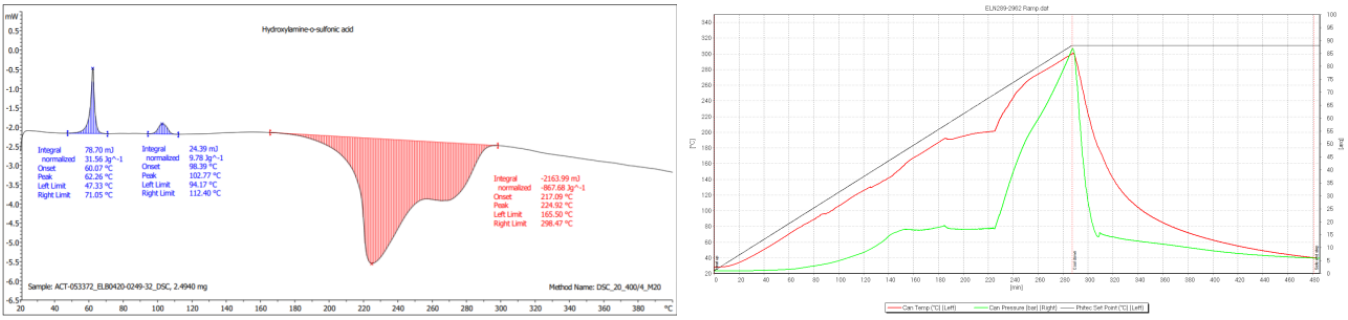


Figure 2. Left graph: DSC of commercial HOSA batch. Endothermic events: blue; exothermic events: red. Right graph: Adiabatic calorimetry analysis of reaction mixture after HOSA addition. Heat rate: 1 °C/min. Max. Temp: 300 °C. adiabatic calorimetric measurement overview; green = can pressure curve. Red = can (internal) temperature curve. *x*-axis: time in minutes; right *y*-axis: temperature in °C; left *y*-axis: pressure in bar. See the SI for further information.

achieved after 16 h. After quenching the reaction mixture with Na_2SO_3, adjusting the pH to 7 with 16% aq. NaOH and addition of product seeds, crystallization of **1** was observed. Cooling of the slurry to 0 °C followed by filtration led to the isolation of **1** as a white solid in 164% uncorrected yield on 10 g scale. The isolated product had a low w/w%-potency (36% w/w by ^{1}H NMR) due to residual salt contamination (mainly Na_2SO_4). Recrystallization of this first crop from hot water vastly improved the assay purity (98% w/w) of **1** at the cost of the overall isolated yield (46%). We speculated that extracting the product into an organic solvent, followed by aqueous washings of the organic phase, would most likely be beneficial in lowering the salt contamination of **1**. Indeed, addition of iPrOAc (10 vol) followed by phase split and washing of the organic phase with H_2O (2.5 vol) worked well to remove the salts prior to crystallization. A solvent switch of the organic layer to cyclopentyl methyl ether (CPME) led to a nice crystallization of **1** in 67% yield on 10-gram scale (98% w/w purity).

PROCESS SAFETY AND FIRST SCALE UP

Prior to engaging into a first scale up run, we performed a first process safety assessment (see the SI for all measurements). While the starting material **2** and the product **1** were of no safety concerns, HOSA is known to be a highly energetic compound. Differential scanning calorimetry (DSC) analysis of a commercial HOSA batch showed two minor endothermic events at 47 °C (−32 kJ/kg) and 94 °C (−10 kJ/kg). A major decomposition with release of a significant amount of energy (868 kJ/kg) started at 166 °C (Figure 2, left graph). The reaction mixture (**2** and 1.3 equiv 1 M aq. NaOH in *t*-BuOH) after addition of 70% aq. *t*-BuOOH (2.0 equiv) showed a mild

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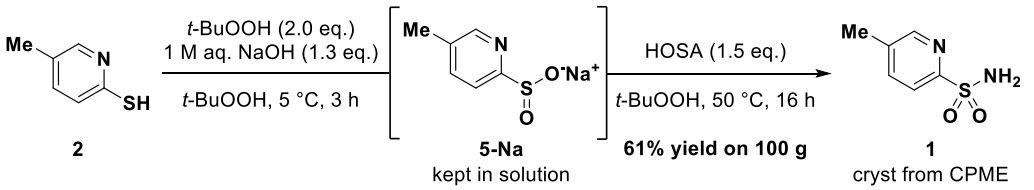
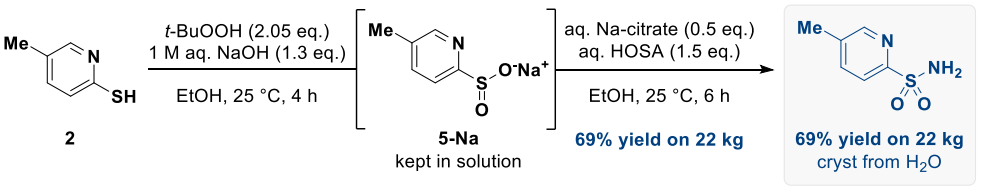
Scheme 3. New HOSA-Route to 1, 100 g Scale Up



Scheme 4. New HOSA-Route to 1, Final 22 kg Production



decomposition event starting at 156 °C (52 kJ/Kg). This was no major safety concern, as the oxidation step was planned to be performed below 30 °C. The reaction mixture after addition of HOSA (1.5 equiv) showed a first, broad endothermic event (−97 kJ/kg) at 93 °C and then a mild exothermic event at 183 °C (30 kJ/kg), also far above the reaction temperature of 50 °C.

It was decided to further analyze the same reaction mixture after addition of HOSA at 0 °C in an adiabatic calorimeter (PhiTec) (Figure 2, right graph). After addition of HOSA (1.5 equiv) at 0 °C, the reaction mixture was rapidly transferred into a Hastelloy bomb and the measurement was immediately started (heat ramp: 25−300 °C, heat rate: 1 °C/min). The Phi-Tec heating ramp measurement showed a slow pressure increase starting from IT = 70 °C (bp *t*-BuOH: 82 °C) together with two minor exothermic events between 90 and 160 °C. The first major sudden pressure increase (from ca. 15−85 bars) and exothermic event started at 200 °C. After cooling down the bomb to RT, a residual pressure of 5−6 bar was measured, which indicated the formation of non-condensable gases. Assuming an aqueous heat capacity of ca. 4 kJ/(kg K), a decomposition event at 200 °C would lead to an estimated Time to Maximum Rate Under Adiabatic Conditions (TMR_{ad}) of over 300 h for a reaction at max IT = 50 °C. Taking these process safety measurements into account, we deemed the reaction safe to run on a larger scale.

A 100 g scale up run was performed in a 10 L double-jacketed glass reactor (Scheme 3). The 70% aq. *t*-BuOOH solution (2.0 equiv) was added slowly over 1 h to a solution of thiophenol **2** and 1 M aq. NaOH (1.3 equiv) in *t*-BuOH (5 vol), while keeping IT below 15 °C. After reaching the IPC limit for **2** (NMT < 3%), HOSA (1.5 equiv) was added as a solid and the reaction mixture was warmed to IT = 45−50 °C and stirred for 16 h. After cooling to RT, the reaction mixture was quenched by addition of solid Na_2SO_3 (0.6 equiv), followed by pH adjustment to pH 7 by 16% aq. NaOH. After the aqueous workup with iPrOAc and a solvent switch of the organic phase to CPME, **1** crystallized as a white solid and was isolated in 61% yield with excellent purity (99% w/w, 99.9% a/a by HPLC).

FINAL ROUTE DEVELOPMENT

While the result of the initial 100 g scale up run was very encouraging, there was clearly room for improvements. The IPC limit for the oxidation step could only be reached after 3 h at 5 °C, as the oxidation was very slow after complete dosing of *t*-BuOOH (95% conv. after addition). The isolated yield was also not as high as expected from the gram-scale experiments. After careful analysis of the aqueous phases and the mother liquor, it was concluded that a significant amount of product was lost during the aqueous wash (2.5 vol) of the iPrOAc phase and in the final mother liquor. In addition, we also realized that after the electrophilic amination step with HOSA, the content of the over-oxidized sulfonic acid was slightly higher than after completed dosing of *t*-BuOOH. This might be the result of sulfinic acid disproportionation or slow oxidation by residual oxidant over time at IT = 45−50 °C, potentially going hand-in-hand with a slow decomposition of HOSA at the elevated reaction temperature. As there was a significant drop in pH after addition of HOSA (from 13.7 to 2.2 after addition, to 1.2 at the end of the reaction), we speculated that buffering the reaction mixture could be beneficial in stabilizing HOSA and favoring the amination reaction at lower temperature.[16] After testing several buffer solutions, adding a 30% aq. sodium citrate solution (0.5 equiv) prior to HOSA addition proved to be optimal (pH ≈ 3 after addition). Not only could the electrophilic amination step be performed at RT, but also a dramatic rate acceleration was observed and full conversion of the sulfinate **5-Na** was achieved within only 3 h. The final IPC purity of **1** was 90.5% a/a by HPLC. To further streamline the process, it was re-attempted to crystallize **1** directly after Na_2SO_3 quench without aqueous workup. To this end, we realized that removal of alcoholic reaction solvent (i.e., EtOH) by distillation after the aq. Na_2SO_3 quench worked well to crystallize **1**. It was very important to keep the aging temperature at 25 °C, as the aqueous solubility of Na_2SO_4 is significantly increased at this temperature compared to 0 °C,[17] therefore limiting the salt contamination of **1**. The described procedure worked well on 10 g scale and **1** was finally isolated as a white solid in 73%

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yield with high purity (99.6% a/a) and minimal salt contamination (ROI: 0.16% w/w).

Prior to transferring this improved process into the production plant, it was assessed if HOSA could also be dosed to the reaction mixture in a controlled manner as an aqueous solution rather than via solid dosage. For safety reasons, the aqueous solution was planned to be freshly prepared at 2 °C in a metal-free reactor. The dissolution of HOSA in water was found to be highly endothermic, but complete dissolution was achieved in only 1.5 vol water (relative to HOSA) at 2 °C. Use-tests showed that this aq. HOSA solution could be kept up to 64 h at IT = 2 °C, while still performing well in the electrophilic amination step (full conversion of **5-Na** after 5 h at 25 °C).[18] As it was now also planned to perform a distillative EtOH removal after the aqueous quench, the stability of this mixture needed to be assessed at elevated temperature. The reaction mixture after Na_2SO_3 quench and neutralization with 32% aq. NaOH was heated to 70 °C and held for 60 h. The final IPC purity over this time frame remained completely unchanged at 90.5% a/a and no new impurities were detected, confirming the stability of the quenched reaction mixture at the foreseen distillation temperature.

The improved HOSA process was performed on 22 kg scale (Scheme 4). The dosage of 70% aq. *t*-BuOOH (2.05 equiv) to a solution of thiophenol **2** in EtOH (5 vol)/1 M aq. NaOH (1.3 equiv) was performed slowly over 4 h, while keeping IT = 25 °C during the addition. IPC showed >99% conversion of **2** and **5-Na**:**6-Na** ratio of 96:4. A 30% aq. Na-citrate dihydrate solution (0.5 equiv) was added as the buffer. Then, the freshly prepared aqueous HOSA solution (1.5 equiv) was dosed over 1.5 h at IT = 25−29 °C. 7 h post addition, IPC confirmed >99% conversion of intermediate **5-Na** to **1**, with a final **6-Na** content of 7.6% a/a. The reaction mixture was quenched with a 20% aq. Na_2SO_3 solution (0.1 equiv), followed by pH adjustment to pH = 8−9 with 32% aq. NaOH. EtOH was removed by distillation and the reactor content warmed to IT = 65−70 °C to achieve complete dissolution. The clear aqueous solution was then cooled to IT = 20−25 °C over 4 h during which time **1** nicely crystallized. The slurry was aged at IT = 20−25 °C for 2 h prior to isolation via centrifugation and cake wash (1 vol H_2O). The desired product was isolated as a white, crystalline solid in 69% yield (20.9 kg) with excellent purity (>99.9% a/a by GC & HPLC; 99.4% w/w by GC assay) and minimal salt contamination (ROI: 0.12% w/w).

In summary, we have developed a vastly improved, sustainable production route for 5-methyl-2-pyridinesulfonamide (**1**) from 5-methylpyridine-2-thiol (**2**). The process employs aq. *t*-BuOOH as a green, chlorine-free oxidant in combination with HOSA as an inexpensive, electrophilic ammonia source. A green solvent mixture (EtOH/H_2O) was used in the process and **1** was isolated by crystallization in excellent purity without the need for any aqueous workup or extractions. The yield was more than doubled (from 29% to now 69%) compared to the original process (Scheme 1). We believe that after further minor process improvements, such as reducing the aqueous volumes and tighter specs on residual EtOH after distillation, the yield can be even further increased. Based on the 22 kg production run, we foresee the HOSA process being able to reduce the batch cycle time by 50% and lower the generated waste by more than 65% (from over 130 kg to 48 kg waste per kg **1**) compared to the sulfonyl chloride chemistry.

EXPERIMENTAL SECTION

General Information. All commercially available materials and solvents were used as received. All Gram-scale experiments were performed in standard laboratory glass wear with magnetic stirrers and under a N_2-atmosphere. All other reactions were run in double-jacketed glass reactors or glass-lined reactors flushed with N_2. Reaction temperatures are expressed as ET = external temperature (e.g., reactor jacket) or IT = internal temperature (temperature of reaction mixture). IPC analyses by LC/MS for intermediates and final product were conducted on a Waters Acquity UPLC instrument using an Agilent Zorbax RRHD SB-aq column (2.1 × 50 mm, 1.8 μm) or Agilent 1260 Infinity II HPLC instrument using a Waters XSelect C18 column (4.6 × 150 mm, 3.5 μm). The mobile phase consisted of two eluents: A: Water/TFA 100:0.04 (v/v) and eluent B: Acetonitrile for UPLC, or A: Water/TFA 100:0.05 (v/v) and eluent B: Acetonitrile/TFA 100:0.05 (v/v) for HPLC. ^{1}H NMR and ^{13}C NMR were measured on a Bruker Ultrashield 400 MHz, 100 MHz. Chemical shifts are expressed in parts per million (ppm) downfield from residual solvent peaks and coupling constants are reported in Hertz (Hz). Splitting patterns are indicated as follows: s, singlet; m, multiplet. Melting point was determined by DSC.

*5-Methyl-2-pyridinesulfonamide (**1**).* To a 2′500 L glass-lined reaction vessel was added purified water (210.0 kg) and 32% NaOH (28.0 kg), followed by addition of 5-methylpyridine-2-thiol **2** (22.05 kg) at 21 °C. The vessel was inertized with nitrogen and ethanol (87.0 kg) was added. IT of the reaction vessel was adapted to 25 °C and a clear solution was obtained. To the mixture was added 70% aq. *t*-BuOOH solution (45.0 kg) over 4 h while maintaining IT = 24.9−26.5 °C. After stirring for 2 h, IPC by HPLC indicated 100% conversion of **2** (acceptance criteria ≥99%), with **6-Na** content of 4.1% a/a. To the reaction mixture was added a 30% aq. sodium citrate solution (prepared from 26.0 kg of sodium citrate dihydrate and 60.2 kg of purified water) over 6 min at IT = 25 °C, followed by slow addition of aq. HOSA solution (prepared from 29.85 kg of HOSA and 44.0 kg of purified water and kept at IT = 0−8 °C) at IT = 25−29 °C. After stirring for 7 h at IT = 25−29 °C, IPC by HPLC indicated 99% conversion of **5-Na**, with **6-Na** content of 7.6% a/a. To the reaction mixture was added slowly 20% aq. Na_2SO_3 (8.80 kg, prepared from 1.80 kg of Na_2SO_3 and 7.0 kg purified water) at IT = 24 °C. Absence of peroxides was confirmed by strip test. 32% NaOH (33.5 kg) was added slowly until pH = 9 at IT = 25 °C. After stirring for 1 h at IT = 25 °C, the reaction mixture was heated up to IT = 42 °C and stirred for 1 h. Subsequent distillation was performed at ET = 56−58 °C (IT = 35−40 °C) under vacuum (127−77 mbar) until distillation target was met (target remaining volume: 15−17.5 vol; 116.0 kg of distillate was collected). The remaining suspension was heated up to IT = 66 °C (solid dissolved), followed by slow cooling to IT = 24 °C over 4 h and final aging at IT = 20 °C for 2 h. Centrifugation of the suspension resulted in a mother liquor of 432.5 kg. Rinsing of the wet cake with 22.0 kg of purified water, followed by drying under vacuum (∼ −0.09 MPa) at 55 °C for 20 h delivered **1** (20.88 kg, 69.0% yield) as a white, crystalline solid. HPLC purity: >99.9 a/a. GS Assay purity: 99.4% w/w. m.p. 131 °C (DSC); ^{1}H NMR (400 MHz, d_6-DMSO) δ 8.54 (s, 1H), 7.86−7.81 (m, 2H), 7.38 (s, 2H), 2.38 (s, 3H); ^{13}C NMR (100 MHz, d_6-DMSO) δ 157.3, 149.7,

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138.3, 136.6, 120.0, 17.8. HRMS (ESI) m/z calcd for $C_6H_9N_2O_2S$ ($[M + H]^+$): 173.0379. Found: 173.0378.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.oprd.3c00131.

Analytical data (NMR, DSC, XRPD) for **1** and process safety of the oxidation/electrophilic amination steps (PDF)

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Notes

The authors declare no competing financial interest.

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accompanied with strong foaming. The reaction then also stalled at ca. 30% conversion of **5-Na**.
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(18) Redox decomposition of the aq. HOSA solution will take place over time to form H_2SO_4, NH_3 and N_2. It has not been tried to store this solution longer than 65 hours at 2 °C. Due to the slow decomposition, storage for extended amount of time, especially at elevated temperatures, is not recommended for quality and safety reasons.

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