ORGANIC PROCESS RESEARCH & DEVELOPMENT
OPR&D
Article
Cite This: Org. Process Res. Dev. XXXX, XXX, XXX−XXX
pubs.acs.org/OPRD

Nitration Using Fuming HNO_3 in Sulfolane: Synthesis of 6-Nitrovanillin in Flow Mode

Souvik Rakshit,[†] Thirumalai Lakshminarasimhan,[†] Sivakrishna Guturi,[†] Kishorekumar Kanagavel,[†] Umamaheswara Rao Kanusu,[†] Ankita G. Niyogi,[†] Somprabha Sidar,[†] Michael R. Luzung,[‡] Michael A. Schmidt,[‡] Bin Zheng,[‡] Martin D. Eastgate,[‡] and Rajappa Vaidyanathan*[,†]

[†]Chemical Development and API Supply, Biocon Bristol-Myers Squibb Research and Development Center, Biocon Park, Jigani Link Road, Bommasandra IV, Bangalore 560099, India

[‡]Chemical and Synthetic Development, Bristol-Myers Squibb, 1 Squibb Drive, New Brunswick, New Jersey 08903, United States

ABSTRACT: We report herein an improved synthesis of 6-nitrovanillin, an important building block used in pharmaceuticals and agrochemicals. The key step in this sequence is the nitration of *O*-Bn vanillin, which was carried out using fuming HNO_3. Sulfolane emerged as the solvent of choice for this transformation due to its high stability toward strongly acidic and oxidizing conditions. The specific hazards of this reaction were studied, and the nitration was efficiently and safely conducted leveraging flow conditions.

INTRODUCTION

6-Nitrovanillin (**1**)[1] is a valuable building block that can be utilized to construct several biologically active natural products and pharmaceutical ingredients (some examples shown, Figure 1).[2−4] Despite its potential as a key intermediate, to the best of our knowledge there are no reports that detail the preparation of this molecule on a large-scale. In a recent program, we were required to synthesize multiple kilograms of 6-nitrovanillin (**1**) for further elaboration; this warranted the development of a robust process for its production.

Direct nitration of vanillin is known to afford 5-nitrovanillin.[5] However, protection of the hydroxyl group redirects the selectivity of the process to produce 6-nitrovanillin.[4,6] Previous reports demonstrated that benzylation followed by nitration and debenzylation affords 6-nitrovanillin (Scheme 1).[6] The key step in this sequence was the nitration of *O*-Bn vanillin **2** using fuming nitric acid. While it may appear straightforward, this reaction was fraught with liabilities which required systematic investigation and resolution before the reaction could be conducted on-scale. For instance, the use of fuming nitric acid with organic solvents mandated a thorough interrogation of their mutual compatibility. Furthermore, the reaction mass containing excess nitrating agent and a potentially energetic product can pose a thermal risk, which can be exacerbated by the presence of polynitrated byproducts, which are likely to form due to the electron-rich nature of the substrate under these conditions.[7]

RESULTS AND DISCUSSION

The benzylation reaction was effected cleanly by treating vanillin with benzyl bromide and K_2CO_3 in acetonitrile (Scheme 2). The resulting *O*-Bn vanillin **2** was subjected to the nitration reaction under a variety of conditions.

The nitration of *O*-Bn vanillin **2** is known in the literature and has been reported on a small scale in several solvents such as dichloroethane, acetic acid, and water, all providing the nitrated product in modest yields.[6] A rapid screen of nitrating agents revealed that the reaction went to completion (as designated by the absence of remaining starting material) only when fuming HNO_3 (98%) was used (entries 1 and 2, Table 1). In both of these cases, the desired nitro product **3** was observed in ∼75−80 area % (by HPLC), along with ∼20 area % of the ipso substitution product **4**,[8] presumably formed via nitration para to the −OBn substituent, followed by deformylation. Most other nitrating agents such as KNO_3 (entry 3), $NaNO_3$ (entry 4), and dilute versions of HNO_3 (entries 5, 6, and 7) provided incomplete conversions. Interestingly, the use of concentrated HNO_3 (70%) with sulfuric acid or trifluoroacetic acid[9] led to complete decomposition of the starting material **2** (entries 8 and 9). This initial screen led us to conclude that fuming HNO_3 was the best nitrating agent out of those studied. However, the documented incompatibility of nitric acid with most organic solvents (e.g., acetic acid) was an issue preventing further scale up.[10]

Our initial approach to synthesize small quantities (<10 g) of **1** for evaluation of subsequent transformations utilized 2 equiv of fuming HNO_3 in MeCN at ∼55 °C (Scheme 3).[11] While this was a reasonable approach for accessing lab scale quantities, both ARSST (Figure 2) and DSC (Figure 3) studies indicated significant thermal events in the vicinity of the operating temperature (55 °C). As seen from the DSC thermograms in Figure 3, the reaction mass with 2 equiv of fuming HNO_3 exhibited an onset temperature of ∼71 °C, with an energy release of 464 J/g (Figure 3a). We hypothesized that we may be able to lower the reaction temperature (and therefore widen the safety margin for the process) by increasing the stoichiometry of the nitric acid, cognizant of the potential for greater energy release due to the presence of excess oxidant in the system. While the reaction proceeded to ca. 65% conversion at room temperature with 8−10 equiv of fuming HNO_3, the increase in nitric acid also lowered the onset temperature, with the expected increase in decomposition energy (Figure 3b and 3c), negating any potential safety advantages.

Received: January 22, 2018

DOI: 10.1021/acs.oprd.8b00020
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

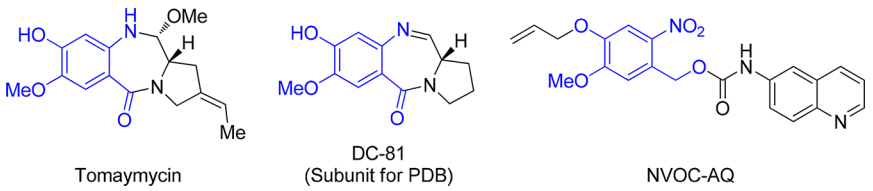
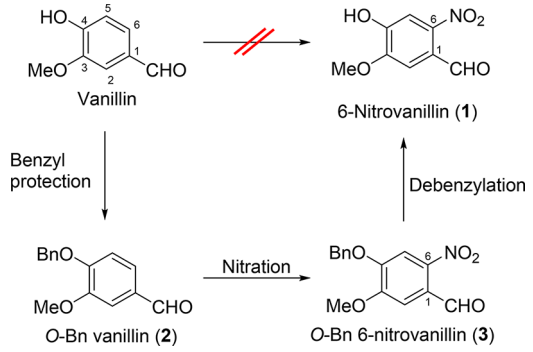
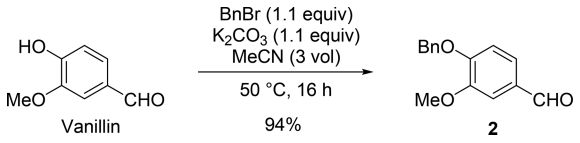


Figure 1. Some bioactive molecules derived from 6-nitrovanillin.

Scheme 1. Known Synthesis of 6-Nitrovanillin



Scheme 2. Benzylation of Vanillin

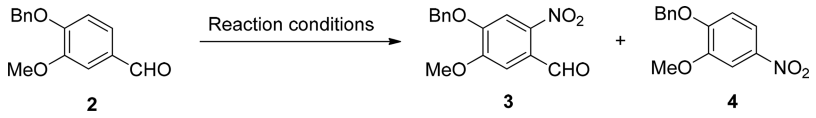


The incompatibility of fuming HNO_3 with acetonitrile as well as with alcohols, ethers, ketones, haloalkanes, and DMSO is well-documented[10] and prompted the quest for a solvent that would be compatible with this challenging reagent. The ideal solvent would have to be inert under the reaction conditions (i.e., it should not be prone to oxidation or trigger thermal events), should be miscible with HNO_3, should preferably solubilize the starting material, and should allow for easy isolation of the product. DSC analysis of mixtures of fuming HNO_3 in acetonitrile, dichloromethane,[12] *N*-methylpyrrolidone, and sulfolane (10% w/w) was carried out. It was found that the mixture of fuming HNO_3 and sulfolane showed a relatively high onset of decomposition (~153 °C) and a significantly lower decomposition energy (~250 J/g) when compared to other mixtures as depicted in Figure 4.

Sulfolane is a highly stable and attractive alternative to common dipolar aprotic solvents such as DMSO, DMF, DMAc, and NMP.[13,14] Because of its high stability toward strong acids and oxidizing agents, as well as its thermal stability, sulfolane is a solvent that can be utilized under a wide range of reaction conditions. Sulfolane has been used as a solvent for aromatic nitration reactions using nitronium tetrafluoroborate ($[NO_2]BF_4$) as a nitrating reagent.[15] However, to the best of our knowledge, there are no reports of the use of sulfolane in combination with concentrated or fuming HNO_3.

Thus, treatment of **2** with 3 equiv of fuming HNO_3 in sulfolane at 35 °C led to complete conversion of starting material within 3 h (entry 1, Table 2). The reaction time could be decreased to 1 h using 5 equiv of fuming HNO_3 to achieve similar conversion (entry 2, Table 2). In both of these instances, the ipso product **4** was formed to the same extent (~22%), which was effectively purged in the downstream operations (vide infra). The high miscibility of sulfolane in water enabled direct precipitation of

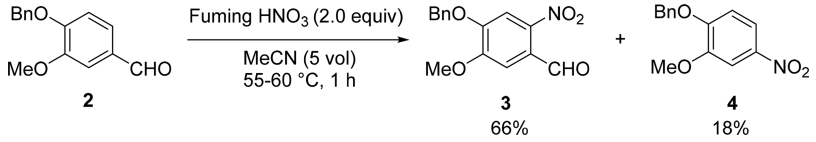
Table 1. Screening of Reaction Conditions for the Nitration Reaction



entry	conditions[a]	IPC[b] (HPLC area %) 2	3	4
1	Fuming HNO_3 (5 equiv), AcOH (5 vol), 23 °C, 8 h	0.2	79.3	17.0
2	Fuming HNO_3 (5 equiv), CH_3CN (5 vol), 55 °C, 1 h	0.2	75.0	19.4
3	KNO_3 (2 equiv), AcOH (8 vol), 0 °C, 16 h	99.3	ND	ND
4	$NaNO_3$ (2 equiv), AcCl (1 equiv), DMF (8 vol), 23 °C, 20 h	32.1	0.1	ND
5	Conc. HNO_3 (10 vol), neat, 0 °C, 2 h	59.0	25.2	3.4
6	Conc. HNO_3 (25 equiv), DCM (5 vol), 0 °C, 2 h	56.8	34.2	6.9
7	Conc. HNO_3 (5 equiv), AcOH (8 vol), 23 °C, 8 h	24.2	59.2	12.9
8	Conc. HNO_3 (2 equiv), H_2SO_4 (8 vol), 0 °C, 2 h	ND	ND	ND
9	Conc. HNO_3 (2 equiv), TFA (8 vol), 23 °C, 2 h	0.9	25.3	ND

[a]All reactions were performed on a 100 mg scale. [b]In-process control (IPC) area % was determined by HPLC at 210 nm.

Scheme 3. Nitration Using Fuming HNO_3 with MeCN



DOI: 10.1021/acs.oprd.8b00020
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

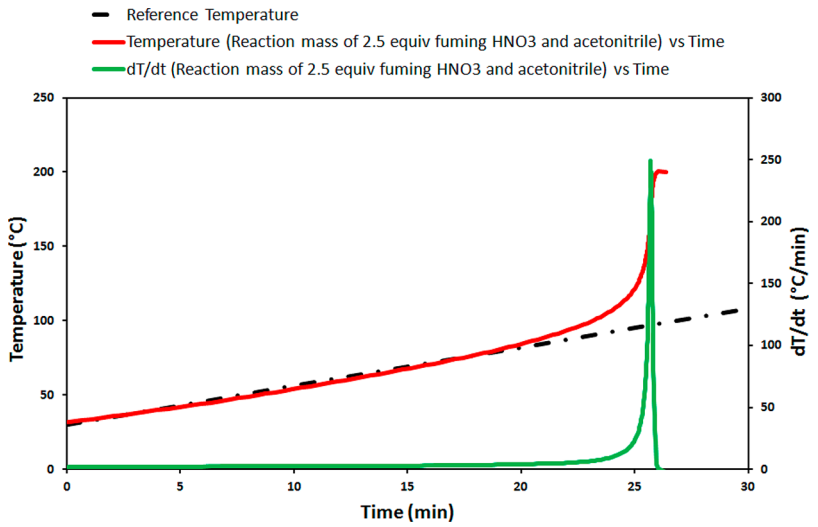


Figure 2. ARSST run—Reaction mixture containing **3** with fuming HNO_3 (2.5 equiv) in MeCN.

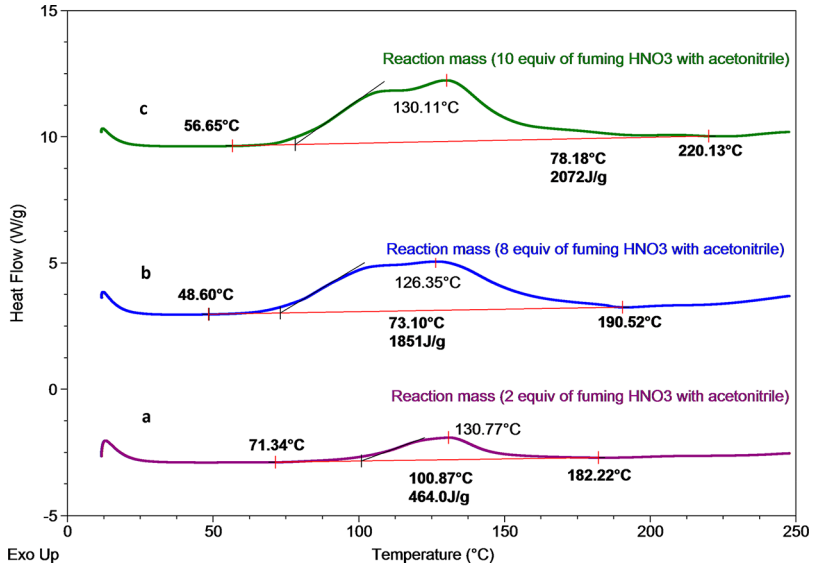


Figure 3. DSC thermograms of reaction mixture containing **3** with fuming HNO_3 in MeCN.

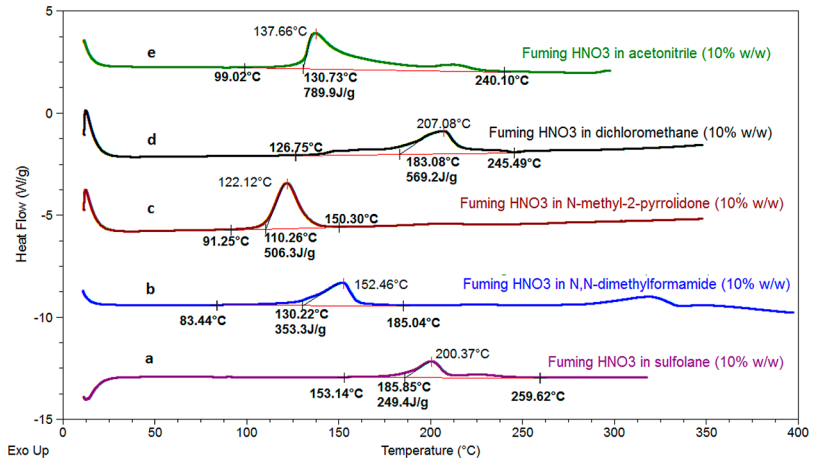


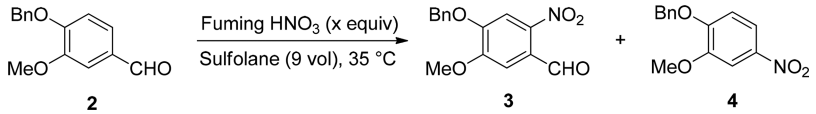
Figure 4. DSC thermograms of fuming HNO_3 in various solvents (10% w/w).

the product by quenching the reaction mass in water, obviating the need for an extractive workup.

In preparation for scale-up of this process in batch mode, we conducted preliminary safety assessments. The reaction seemed to perform best with 10 mL of sulfolane per gram of **2**. This concentration was achieved by dissolving **2** in 7 vol of sulfolane and by utilizing the remaining 3 vol of sulfolane to prepare a 25% w/w solution of nitric acid (5 equiv of fuming HNO_3).

DOI: 10.1021/acs.oprd.8b00020
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

Table 2. Optimization of Equiv of Fuming HNO_3 for Nitration Reaction



2 3 4

	conditions[a]		IPC[b] (area %)		
entry	equiv of HNO_3	time (h)	2	3	4
1	3	3	ND	70.9	21.4
2	5	1	ND	76.7	22.1

[a]All reactions were performed on a 100 mg scale. [b]In-process control (IPC) area % was determined by HPLC at 210 nm.

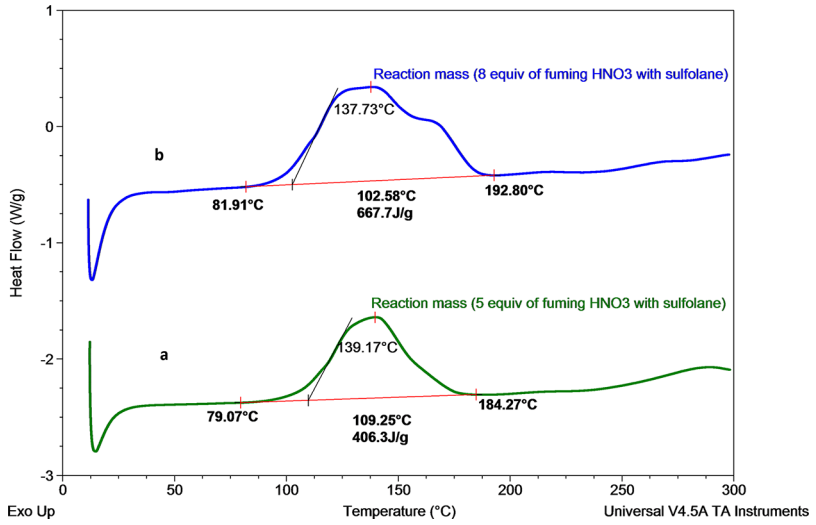


Figure 5. DSC thermogram of nitration reaction mass.

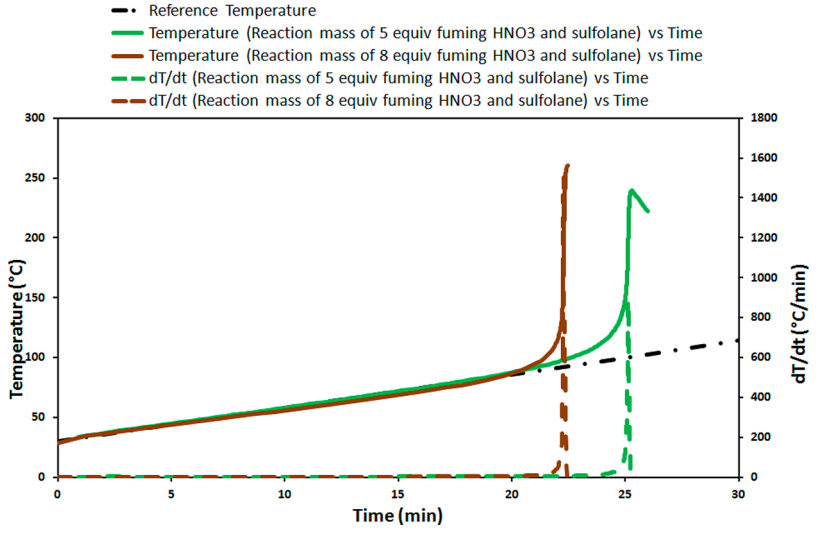


Figure 6. Temperature and self-heating profile of nitration reaction mass in ARSST.

Dilution of fuming HNO_3 using sulfolane was found to be exothermic (RC1e) with an adiabatic temperature rise of 35 °C. The HNO_3/sulfolane solution was charged dropwise into the solution of starting material **2** in sulfolane while maintaining the reaction temperature below 38 °C. As expected, the nitration was found to be exothermic (energy of −160 kJ/mol) with an adiabatic temperature rise of 31 °C. The reaction was found to be dose controlled, with 80% of the total heat evolved during the addition. The thermal stability of the reaction mass was evaluated by DSC and ARSST, and onset of a significant exotherm was observed around 80 °C (Figure 5a and the green lines in Figure 6) with an energy release of 406 J/g (adiabatic temperature rise (ΔT_{ad}) of ~270 °C).

Kinetic analysis of the heat data from DSC using AKTS software[16] predicted the ADT24[17,18] to be 45 °C (Figure 7), which was in close agreement with the estimated ADT24 using the self-heating data from the ARSST[19] run (42 °C). This relatively low ADT24 suggested a high probability of decomposition or a thermal runaway reaction in the case of loss of temperature control (either due to loss of control on external cooling, or addition rate) during the reaction. This could possibly trigger secondary decomposition reactions (MTSR > ADT24),

DOI: 10.1021/acs.oprd.8b00020
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

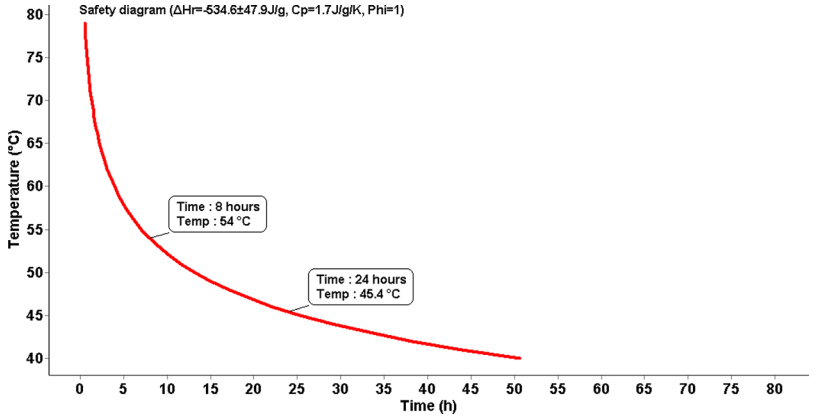


Figure 7. Thermal stability diagram of reaction mass after the formation of **3**.

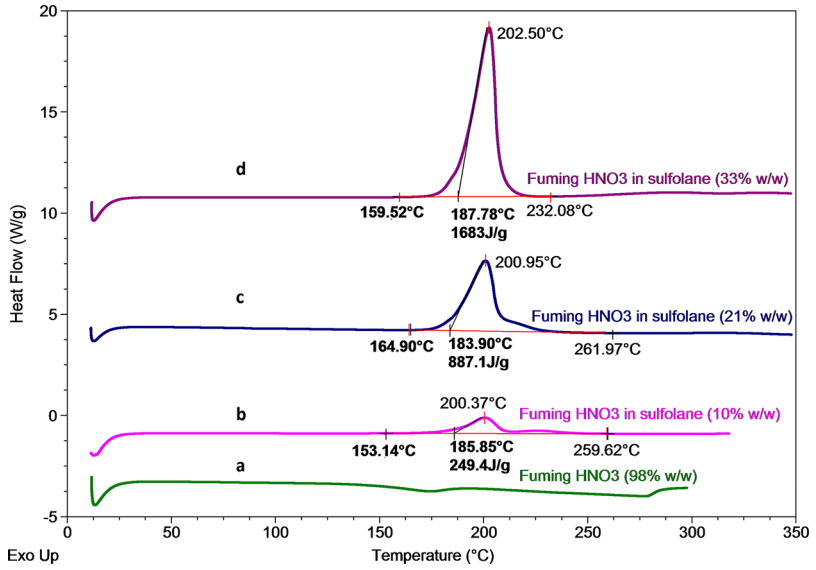


Figure 8. DSC thermograms of fuming HNO_3–sulfolane solution at various concentrations.

and the process would fall into Stoessel Criticality Class 5,[18] indicating severe risks. A safety review of the process indicated that batch mode would not be a viable long-term option due to the narrow thermal operating window, and thus, we explored the feasibility of carrying out the nitration reaction in flow mode.[20,21]

The fact that the nitration reaction in sulfolane was homogeneous was a major advantage that made it amenable for execution in flow. However, the relatively long reaction time using 5 equiv of fuming HNO_3 (~1 h) could limit this option (Table 2). In an effort to increase the reaction rate, the process was attempted using 8 equiv of fuming HNO_3 on a small scale in the laboratory. Gratifyingly, the reaction reached complete conversion within 15 min at 40 °C. Encouraged by these results, we evaluated the thermal stability of the fuming HNO_3–sulfolane solution (8 equiv of fuming HNO_3 in 3 vol of sulfolane per g of **2**, which translates to ~33% w/w fuming HNO_3 in sulfolane). DSC analysis of varying concentrations of HNO_3 in sulfolane revealed that while the onset temperature did not vary significantly with increasing concentrations (remaining close to ~160 °C), the severity of decomposition, i.e. energy released, increased significantly, as seen previously. As depicted in Figure 8, a solution of 10% w/w fuming HNO_3 in sulfolane shows an energy of ca. 250 J/g, while the 33% w/w solution exhibits an energy of 1683 J/g.[22]

The 33% w/w fuming HNO_3-sulfolane mixture was found to be stable in the operating conditions by kinetic analysis of DSC data using AKTS software (ADT24 = 91 °C).[23] Samples of reaction mixtures containing excess nitric acid (8–10 equiv used for the reaction) were tested in DSC and ARSST and were found to exhibit onset of severe exotherm/self-heating at ~80 °C (Figure 5b and the brown lines in Figure 6). The 1 h Time to Maximum Rate (TMR_{ad}) was found to be 55–65 °C by kinetic analysis of self-heating data from ARSST and DSC heat data by AKTS software, indicating that the mass was stable in the flow conditions as the residence time in the flow reactor was expected to be no more than 15 min.

With these data in hand, a set of screening experiments was performed using the flow reactor (Hastelloy C22, id 0.18 cm, and length 9.1 m). Two inlet streams, namely a 1 M solution of **2** in sulfolane, and a ~33% w/w solution of fuming HNO_3 in sulfolane, were passed through the coiled reactor at a specific temperature (Figure 9; for actual set up, see Experimental Section). The sulfolane solution of **2** was maintained at 35 °C,[24] while the solution of fuming HNO_3 in sulfolane was maintained at room temperature. The outlet stream was quenched by allowing it to flow directly into a vessel containing chilled water (0–5 °C), and the resultant crystalline product was isolated by filtration.

In these screening experiments, it was found that a residence time of 11.3 min at 35 °C led to very good conversions (entry 1, Table 3). Attempts to shorten the residence time by increasing the reaction temperature alone were not successful

DOI: 10.1021/acs.oprd.8b00020
Org. Process Res. Dev. XXXX, XXX, XXX–XXX

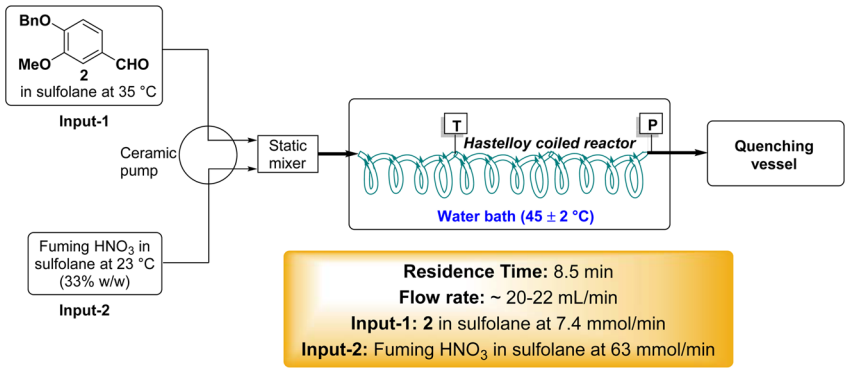


Figure 9. Nitration of **2** in continuous flow mode.

Table 3. Screening Experiments for the Nitration in Continuous Flow Mode

entry	R_t (min)	temp (°C)	equiv of fuming HNO_3	IPC[a] (HPLC area %) 2	3	4
1	11.3	35	8.0	1.9	76.1	21.0
2	3.4	40	8.0	15.5	66.8	17.1
3	4.3	40	8.0	13.9	67.0	18.4
4	8.5	45	8.7	1.3	77.1	21.6

[a]In-process control (IPC) area % was determined by HPLC at 210 nm.

(entries 2 and 3, Table 3). However, increasing both the temperature and the stoichiometry of HNO_3 led to high conversions and shortened the residence time to 8.5 min (entry 4, Table 3). These conditions were validated on a 2 kg scale (Figure 9) and afforded the product in ∼70% assay corrected yield at a satisfactory production rate of ∼110 g/h (see Experimental Section).

The solids isolated after filtration were washed with water to remove traces of sulfolane and dried in a vacuum tray dryer at 45−50 °C. Compound **3** thus isolated was found to be energetic, displaying an onset of a major exotherm at ∼226 °C (energy = 1246 J/g), by DSC but was found not to be shock or friction sensitive.[25] The compound was found to be stable in the operating conditions (AKTS software predicted an ADT24 of 158 °C, which is well above the drying temperature of 45−50 °C required for complete removal of water).

Crude **3** isolated from the nitration reaction contained ca. 20% of the ipso impurity **4**. Treatment of this mixture with trifluoroacetic acid (2.5 vol) in CH_2Cl_2 (1 vol) at 40 °C for 16 h afforded the debenzylated product **1** in >98 area % purity after crystallization from MTBE. Isolated **1** displayed onset of a severe event around 195 °C with an average energy of 1977 J/g. Although the compound was energetic, it was found isolable as it was not sensitive to impact and friction.[25] The overall process is depicted in Scheme 4. The benzylation−nitration−debenzylation sequence was accomplished on a multikilogram scale to provide **1** in 62% yield and >98% purity.

CONCLUSION

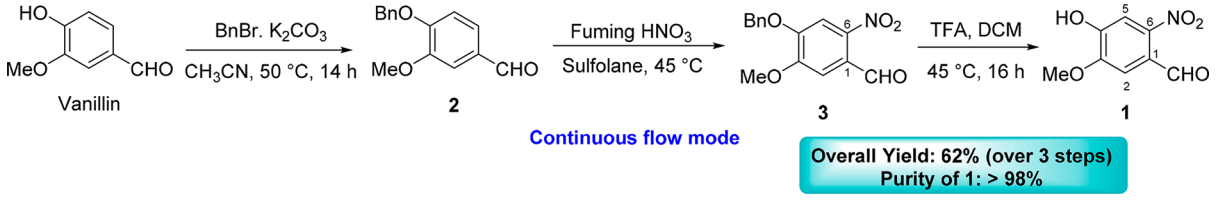
In conclusion, we have developed a safe, robust, and scalable protocol for the synthesis of 6-nitrovanillin. The key step in this sequence was the nitration of *O*-Bn vanillin on large-scale to selectively afford the 6-nitro analog. The best reagent for this transformation was fuming nitric acid; however, the incompatibility of this reagent with various organic solvents was a serious limitation that needed to be overcome prior to scale-up. Sulfolane emerged as the solvent of choice for this transformation: it was stable under the reaction conditions, provided good solubility of the starting material, and allowed for easy isolation of the product. The process safety hazards associated with the use of fuming nitric acid on large-scale were overcome by carrying out the transformation in flow mode. To the best of our knowledge, this is the first report of the successful use of sulfolane in conjunction with nitric acid.

EXPERIMENTAL SECTION

General. All reactions were performed under a nitrogen atmosphere. Commercial reagents were used as received. Anhydrous fuming nitric acid (98%) was procured from Avra. Sulfolane (LR grade) was procured from Spectrochem. Chemical shifts for protons are reported in parts per million downfield from tetramethylsilane and are referenced to residual proton in the NMR solvent ($(CD_3)_2SO$ = δ 2.50). Chemical shifts for carbons are reported in parts per million downfield from tetramethylsilane and are referenced to the carbon resonances of the solvent ($(CD_3)_2SO$ = δ 39.5).

4-Hydroxy-3-methoxybenzaldehyde (2). Acetonitrile (1.6 L) was charged to a reactor and heated to 40 °C. Vanillin (4.0 kg, 26.3 mol) was charged to the solvent at 40 °C under nitrogen atmosphere. Potassium carbonate (4.0 kg, 28.9 mol) was charged lot wise by maintaining the temperature of the reaction at 40−45 °C. Benzyl bromide (3.4 L, 28.9 mol, 1.1 equiv) was added dropwise over 15−20 min under nitrogen. After the addition was complete, the reaction mass was heated to 50 °C and maintained at the same temperature for 12−14 h. After reaction completion,

Scheme 4. Overall Scheme for the Synthesis of 6-Nitrovanillin (1)



DOI: 10.1021/acs.oprd.8b00020
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

the reaction mass was cooled to 0−5 °C and chilled water (40 L) was slowly added to it (white crystalline product precipitated out). The resulting slurry was stirred at 0−5 °C for ∼2 h, filtered and the cake was washed with purified water (20 L), followed by *n*-heptane (20 L). The isolated solid was dried at 40 °C under vacuum to provide 6.0 kg (94% yield) of **2** as a white crystalline solid. ^{1}H NMR (300 MHz, DMSO-d6) δ 9.85 (s, 1H), 7.54 (dd, J = 8.4, 1.8 Hz, 1H), 7.49−7.35 (m, 6H), 7.27 (d, J = 8.1 Hz, 1H), 5.22 (s, 2H), 3.84 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d6) δ 191.3, 153.2, 149.4, 136.3, 129.8, 128.4, 128.0, 127.9, 125.8, 112.6, 109.8, 70.0, 55.5.

Nitration of O-Bn vanillin (2) with fuming HNO_3 in continuous flow mode using a plug flow reactor. A solution of *O*-Bn vanillin **2** (1.0 kg, 4.1 mol, 1.0 equiv) in sulfolane (4.0 L) was prepared in an all-glass reactor (Reactor-1), and maintained at 30−35 °C.[24] In another similar reactor (Reactor-2), fuming nitric acid (2.3 kg, 36.0 mol, 8.7 equiv) was charged slowly to sulfolane (3.5 L) maintained at 30−35 °C (during the mixing of fuming HNO_3 and sulfolane, a 5−10 °C exotherm was observed). These two solutions were pumped via an FMI-Ceramic pump (Ceram pump), and then through a plug flow reactor (C-22 Hastelloy coil)[26] equipped with a temperature sensor (Hastelloy C) and a pressure gauge. The coil was immersed in a water bath maintained at 45−50 °C. The flow rate of each of the solutions was adjusted to 630 mL/h (10.5 mL/min each). The outlet stream from the plug flow reactor was drained into a glass quenching vessel containing chilled water (20 L) maintained at 5−10 °C. The solid that precipitated in the quenching vessel was filtered, and the filter cake was washed with water (5 L). The solid was unloaded and suspended in a fresh reactor with water (10 L) and stirred for 1 h at 30−35 °C (Note: this reslurry protocol was used to remove traces of sulfolane).[27] The yellow solid mass was filtered, washed with water (5 L) and dried in vacuo at 50−55 °C for 16 h to provide 1.1 kg (71% assay corrected yield) of **3** as a pale yellow solid. The material also contained ∼20% of ipso product **4**. A total of 4.8 kg of crude **3** was synthesized using this protocol at a production rate of ∼110 g/h.

Analytically pure samples of **3** and **4** were isolated by flash column chromatography for characterization purposes (SiO_2, eluent: *n*-heptane:EtOAc 9:1 → 1:1).

4-(Benzyloxy)-5-methoxy-2-nitrobenzaldehyde (or O-Bn-6-nitrovanillin) 3. ^{1}H NMR (400 MHz, DMSO-d6) δ 10.21 (s, 1H), 7.84 (s, 1H), 7.50−7.48 (m, 2H), 7.45−7.42 (m, 2H), 7.40−7.38 (m, 2H), 5.33 (s, 2H), 3.97 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d6) δ 188.4, 152.8, 150.8, 143.3, 135.6, 128.5, 128.3, 128.0, 124.9, 110.1, 108.7, 70.7, 56.4.

1-(Benzyloxy)-2-methoxy-4-nitrobenzene 4. ^{1}H NMR (400 MHz, DMSO-d6) δ 7.90 (dd, J = 8.1, 2.4 Hz, 1H), 7.77 (d, J = 2.4 Hz, 1H), 7.49−7.47 (m, 2H), 7.46−7.37 (m, 3H), 7.28 (d, J = 8.8 Hz, 1H), 5.26 (s, 2H), 3.90 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d6) δ 153.6, 148.8, 140.8, 135.9, 128.5, 128.2, 127.9, 117.4, 112.0, 106.4, 70.4, 55.9.

4-Hydroxy-5-methoxy-2-nitrobenzaldehyde (or 6-nitrovanillin) 1. CH_2Cl_2 (3.9 L) was charged to a reactor followed by crude 4-(benzyloxy)-5-methoxy-2-nitrobenzaldehyde **3** (3.9 kg with 80.7% assay, 13.5 mol assay corrected) and trifluoroacetic acid (9.7 L, 14.6 kg, 128.3 mol). After completion of addition, the reaction mixture was stirred at 40−45 °C for 14−16 h. After reaction completion, the mixture was cooled to 0−10 °C. MTBE (27 L) was charged slowly into the mass over 2 h, maintaining the temperature at 0−10 °C. The resulting slurry was stirred for 1 h at 0−10 °C, filtered, and the cake was washed with chilled MTBE (2 × 7.8 L) at 0−10 °C. The solid was deliquored for 6 h under reduced pressure to provide 2.1 kg of **1** (97.5% potency, 94% assay corrected yield) as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d6) δ 11.01 (brs, 1H), 10.16 (s, 1H), 7.50 (s, 1H), 7.35 (s, 1H), 3.95 (s, 3H): ^{13}C NMR (75 MHz, DMSO-d6) δ 188.2, 151.8, 150.9, 143.7, 123.4, 111.0, 110.6, 56.3.

AUTHOR INFORMATION

Corresponding Author

*E-mail: vaidy@bms.com.

ORCID

Michael R. Luzung: 0000-0001-9729-2211
Michael A. Schmidt: 0000-0002-4880-2083
Bin Zheng: 0000-0002-5466-174X
Martin D. Eastgate: 0000-0002-6487-3121
Rajappa Vaidyanathan: 0000-0002-2236-5719

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

We thank Jayaprakash Karamil and Sabuj Mukherjee for their contributions. Analytical support was provided by Saravanan Natarajan, Periyasamy Palanisamy, and Hemant Bhutani. We thank Simon Leung and Dhinesh Selvam for their assistance with process safety data. Scale-up support from the Bristol-Myers Squibb Chemical Development Laboratory operating staff is gratefully acknowledged. Our sincere thanks are extended to David Kronenthal and Robert Waltermire for their support of this work.

REFERENCES

(1) The numbering followed throughout this paper is based on the vanillin ring system as depicted in Scheme 1. The IUPAC numbering is provided in the experimental section.

(2) Arima, K.; Kohsaka, M.; Tamaru, G.; Imanaka, H.; Sakai, H. *J. Antibiot.* **1972**, *25*, 437. Arora, S. K. *J. Antibiot.* **1981**, *34*, 462.

(3) (a) Kamal, A.; Rao, M. V.; Laxman, N.; Ramesh, G.; Reddy, G. S. K. *Curr. Med. Chem.: Anti-Cancer Agents* **2002**, *2*, 215. (b) Gregson, S. J.; Howard, P. W.; Hartley, J. A.; Brooks, N. A.; Adams, L. J.; Jenkins, T. C.; Kelland, L. R.; Thurston, D. E. *J. Med. Chem.* **2001**, *44*, 737. (c) Thurston, D. E.; Bose, D. S. *Chem. Rev.* **1994**, *94*, 433.

(4) Zhu, B.; Jiang, B.; Na, Z.; Yao, S. Q. *Chem. Commun.* **2015**, *51*, 10431.

(5) For selected examples of the synthesis of 5-nitrovanillin, see: (a) Mondal, M. A.; Mandal, D.; Mitra, K. *J. Chem. Sci.* **2017**, *129*, 39. (b) Chen, H.-z.; Chen, Y.-b.; Lv, Y.-p.; Zeng, F.; Zhang, J.; Zhou, Y.-l.; Li, H.-b.; Chen, L.-f.; Zhou, B.-j.; Gao, J.-r.; Xia, C.-n. *Bioorg. Med. Chem. Lett.* **2014**, *24*, 4367. (c) Kiss, L. E.; Ferreira, H.; Torrão, L.; Bonifácio, M. J.; Palma, P. N.; Soares-da-Silva, P.; Learmonth, D. A. *J. Med. Chem.* **2010**, *53*, 3396. (d) Lalitha, A.; Sivakumar, K. *Synth. Commun.* **2008**, *38*, 1745. (e) Anuradha, V.; Srinivas, P. V.; Aparna, P.; Rao, J. M. *Tetrahedron Lett.* **2006**, *47*, 4933. (f) Bailey, K.; Tan, E. W. *Bioorg. Med. Chem.* **2005**, *13*, 5740. (g) Malecki, N.; Carato, P.; Rigo, B.; Goossens, J.-F.; Houssin, R.; Bailly, C.; Hénichart, J.-P. *Bioorg. Med. Chem.* **2004**, *12*, 641.

(6) For selected examples of the synthesis of 6-nitrovanillin, see: (a) Howard, P. W. *PCT Int. Appl.*, 2014057074, 17 Apr 2014. (b) Janett, E.; Bernardinelli, Y.; Müller, D.; Bochet, C. G. *Bioconjugate Chem.* **2015**, *26*, 2408. (c) Tiberghien, A. C.; Levy, J.-N.; Masterson, L. A.; Patel, N. V.; Adams, L. R.; Corbett, S.; Williams, D. G.; Hartley, J. A.; Howard, P. W. *ACS Med. Chem. Lett.* **2016**, *7*, 983. (d) Tsai, S.-C.; Klinman, J. P. *Bioorg. Chem.* **2003**, *31*, 172. (e) Jin, J.-W.; Zhang, L.; Meng, G.-R.; Zhu, J.-H.; Zhang, Q. *Synth. Commun.* **2014**, *44*, 346. (f) Critchley, K.; Jeyadevan, J. P.; Fukushima, H.; Ishida, M.; Shimoda, T.; Bushby, R. J.; Evans, S. D. *Langmuir* **2005**, *21*, 4554. (g) Lai, Y.-S.; Kao, C. − L.; Chen, Y. − P.; Fang, C. − C.; Hua, C. − C.; Chu, C. − C. *New J. Chem.* **2016**, *40*, 2601.

DOI: 10.1021/acs.oprd.8b00020
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

(7) (a) Gustin, J. L. *Org. Process Res. Dev.* **1998**, *2*, 27. (b) Firth, D. *Innov. Pharm. Technol.* **2000**, *1*, 134. (c) Beutner, G. L.; Desai, L.; Fanfair, D.; Lobben, P.; Anderson, E.; Leung, S. W.; Eastgate, M. D. *Org. Process Res. Dev.* **2014**, *18*, 1812.
(8) (a) Colonna, M.; Greci, L.; Poloni, M. *J. Chem. Soc., Perkin Trans. 2* **1984**, *2*, 165. (b) Collet, C.; Delville, A.; Laszl, P. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 535. (c) Downer, N. K.; Jackson, Y. A. *Org. Biomol. Chem.* **2004**, *2*, 3039. (d) Moodie, R. B.; Schofield, K. *Acc. Chem. Res.* **1976**, *9*, 287.
(9) Kowalczyk, A.; Roberts, P. N.; McEwen, G. K.; Robinson, J., III *Org. Process Res. Dev.* **1997**, *1*, 355.
(10) Urben, P. G. *Bretherick's Handbook of Reactive Chemical Hazards*, 7th ed.; Elsevier, 2007; Vol. *1*, pp 1633.
(11) Wright, O. L.US3221062 A.
(12) CH_2Cl_2-nitric acid has been used in nitrations; see: Knapkiewicz, P.; Skowerski, K.; Jaskólska, D. E.; Barbasiewicz, M.; Olszewski, T. K. *Org. Process Res. Dev.* **2012**, *16*, 1430 However, this combination has been shown to be detonable (see also ref 10).
(13) Tilstam, U. *Org. Process Res. Dev.* **2012**, *16*, 1273.
(14) For use of sulfolane as solvent in continuous flow, see: Tilstam, U. *Org. Process Res. Dev.* **2012**, *16*, 1974.
(15) (a) Olah, G. A.; Kuhn, S. J.; Flood, S. H. *J. Am. Chem. Soc.* **1961**, *83*, 4571. (b) Walker, M. D.; Andrews, B. I.; Burton, A. J.; Humphreys, L. D.; Kelly, G.; Schilling, M. B.; Scott, P. W. *Org. Process Res. Dev.* **2010**, *14*, 108.
(16) Advanced Kinetics and Technology Solutions; www.akts.com.
(17) ADT24 is the temperature at which time to maximum rate under adiabatic condition (TMR_{ad}) is 24 h and the compound has acceptable thermal stability. See Lakshminarasimhan, T. *Org. Process Res. Dev.* **2014**, *18*, 315.
(18) *Thermal safety of Chemical Processes*; Stoessel, F. Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2008.
(19) Theis, A. E.; Burelbach, J. P.; Askonas, C. F. *Process Saf. Prog.* **2009**, *28*, 135.
(20) (a) Porta, R.; Benaglia, M.; Puglisi, A. *Org. Process Res. Dev.* **2016**, *20*, 2. (b) Kulkarni, A. A. *Beilstein J. Org. Chem.* **2014**, *10*, 405.
(21) Brocklehurst, C. E.; Lehmann, H.; Vecchia, L. L. *Org. Process Res. Dev.* **2011**, *15*, 1447.
(22) Negative results were observed in six trials at an impact energy of 60 J, as well as in six trials at a friction force of 240 N (although inflammation was observed at 360 N). As a result, the material is not considered to be impact or friction sensitive.
(23) The Self-Accelerating Decomposition Temperature (SADT) of this solution was predicted to be 74 °C, providing a reasonable thermal window for storage.
(24) The solution of **2** in sulfolane was maintained at 35 °C to prevent the freezing of sulfolane (mp = 28 °C).
(25) Negative results were observed in six trials at an impact energy of 40 J (although crackling was observed at an impact energy of 60 and 50 J), as well as in six trials at a friction force of 360 N. As a result, the material is not considered to be impact or friction sensitive.
(26) Fuming HNO_3 is compatible with Hastelloy, C. See:McConville, F. X. *The Pilot Plant Real Book*, 2nd ed.; FXM: Worcester, MA, 2007; pp 10−22.
(27) The mother liquors after the filtration were neutralized with NaOH prior to disposal.

DOI: 10.1021/acs.oprd.8b00020
Org. Process Res. Dev. XXXX, XXX, XXX−XXX