Article

Development of a Safe and High-Throughput Continuous Manufacturing Approach to 4-(2-Hydroxyethyl)thiomorpholine 1,1-Dioxide

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Ⓢ Supporting Information

ABSTRACT: Continuous processing enabled the highly energetic double conjugate addition of ethanolamine to divinylsulfone to prepare 2 kg of 4-(2-hydroxyethyl)thiomorpholine 1,1-dioxide, as an intermediate in the synthesis of HIV Maturation Inhibitor BMS-955176. In situ IR was employed to monitor the steady state of the transformation for increased robustness via appearance of the thiomorpholine dioxide moiety and disappearance of the divinylsulfone. Surprisingly, a series of oligomers formed as intermediates, which converted to product with extended aging or heating, consistent with computational predictions. By running this process in flow, the highly exothermic reaction could be safely executed in an equal volume of water as the only solvent, despite an adiabatic temperature rise of 142 °C, leading to a streamlined and efficient process.

INTRODUCTION

The development of HIV MI Inhibitor BMS-955176 required the preparation of kilogram quantities of side chain 4-(2-hydroxyethyl)thiomorpholine 1,1-dioxide [CAS: 26475-62-7] (**1**) (Scheme 1).[1] Synthesis from the commodity feedstocks

Scheme 1. Thiomorpholine Dioxide 1 as a Key Building Block for BMS-955176
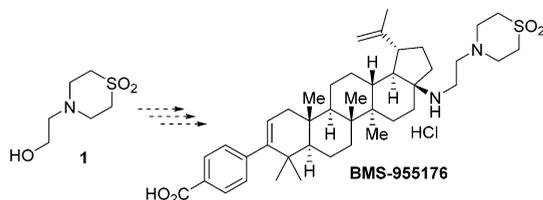
divinylsulfone (DVS) and 1,2-ethanolamine (EA) through double conjugate addition, which had been previously employed on gram scale, appeared to be the most straightforward, efficient, and atom economical approach (Scheme 2).[2] However, a process hazard evaluation prior to implementation on larger scale revealed an exothermic reaction (exp ΔH = 33.9 kcal/mol) with a large adiabatic temperature rise of 79.2 °C (Scheme 2), prompting our team to seek out a safe, scalable method of implementation.[3–5]

Scheme 2. Batch Preparation of 1 from EA and DVS
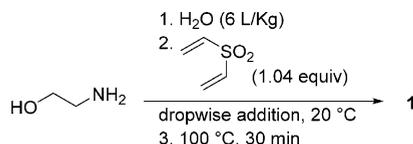
While this batch process was suitable on small scale and could be controlled by slow addition of DVS, it did not appear amenable to large scale production due to excessively long addition times as the surface area to volume ratio decreased. As an alternative, a continuous process was investigated, where the heat generated in the reaction could be readily dissipated due to the high surface area and heat transfer rate, minimizing the chance of an uncontrolled reaction, overpressurization, and thermal degradation or polymerization of DVS. Moreover, a continuous process would minimize exposure to DVS, a toxic alkylating agent.[6,7]

RESULTS AND DISCUSSION

A continuous process was initially investigated on a small scale in a 2 mL glass chip (Uniqsis) containing a static mixer, which was submerged in a 22 °C water bath. Using two syringe pumps, a solution of EA in water (6 vol) was combined with divinyl sulfone (1.04 equiv), with a residence time of 1 min. The reaction stream was collected into D_2O and immediately analyzed by ^{1}H NMR, which showed full conversion of the EA.[8,9] Interestingly, although the EA and >95% of the divinyl sulfone were completely consumed, an unidentified species was observed at a level of 10−20%. Fortunately, in the reaction stream, this species completely converted to **1** within 12 h at 20 °C, or within 10 min at 80 °C. Based on the reactivity and preliminary NMR analysis, it seemed possible that the unknown species could be an open-chain monomer (**2**), dimer (**3**), or higher order oligomer of **1** (trimer **4**, tetramer **5**, etc.), prompting further investigation by LC-MS, NMR, and computational methods (Scheme 3).

Scheme 3. Proposed Intermediates in Conversion of EA and DVS to 1
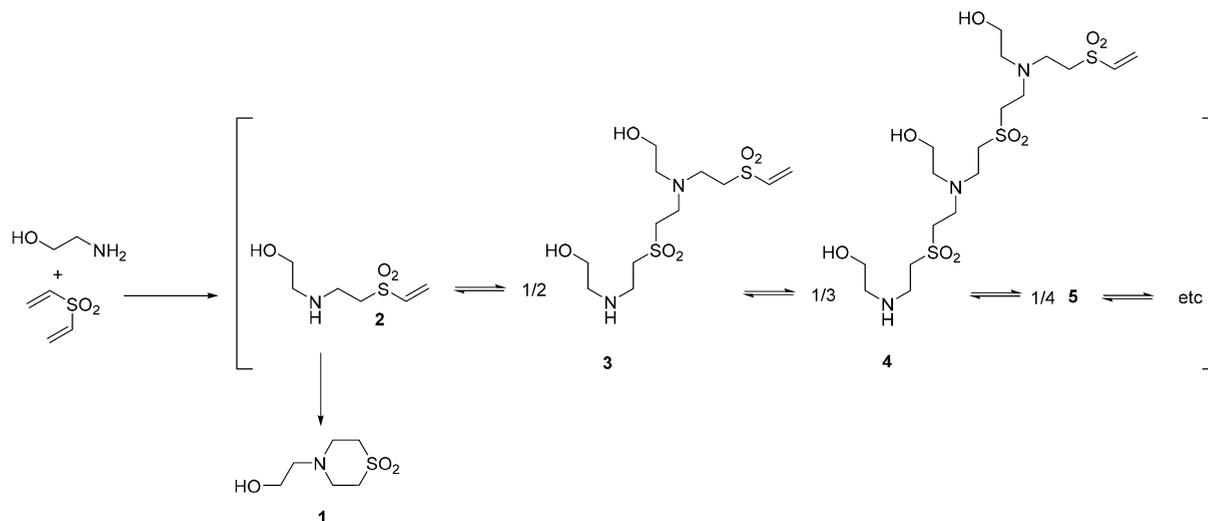
To study the formation of suspected oligomers and rearrangement to product **1**, DVS (1.05 equiv) was added over 20 min to a solution of EA in 3 vol water with the internal temperature maintained below 7 °C to minimize conversion to **1**. Once addition was complete, the solution was heated to 20 °C (t = 0 min) and the progress of the reaction was monitored through ^{1}H NMR analysis of samples (30-fold dilution into D$_2$O). Based on ^{1}H NMR of the reaction mixture at 2 h, the structure is most consistent with trimer **4**, with an ∼36:3 acyclic aliphatic/vinyl proton ratio (32:3 theoretical) (Scheme 3). However, this is not distinguishable from a mixture of both higher and lower order oligomers, which could lead to the same ratio.[10]

LC-MS analysis of the reaction mixture at 2 h showed many adducts of EA and DVS, either in an n:n or n:n+1 ratio, favoring the DVS. No peaks were observed corresponding to structures with greater EA content, possibly due to the excess of DVS used. Table 1 shows the exact masses of the oligomers

Table 1. Oligomers of 1 Observed by LC-MS

oligomer (n:n)	exact mass	RT (min)	oligomer (n:n+1)	exact mass	RT (min)
EA$_1$DVS$_1$ (**1**)	179.1	0.55			
EA$_1$DVS$_1$ (**2**)	179.1	0.65	EA$_1$DVS$_2$	297.1	0.82
EA$_2$DVS$_2$ (**3**)	358.1	0.84	EA$_2$DVS$_3$	476.1	1.86
EA$_3$DVS$_3$ (**4**)	537.2	1.03	EA$_3$DVS$_4$	655.2	2.79
EA$_4$DVS$_4$ (**5**)	716.2	1.43	EA$_4$DVS$_5$	834.3	3.32
EA$_5$DVS$_5$	895.3	2.46	EA$_5$DVS$_6$	1013.3	3.77
EA$_6$DVS$_6$	1074.4	2.95	EA$_6$DVS$_7$	1192.4	4.14

detected, along with the corresponding LC retention times.[11] Additional oligomeric peaks appeared at later retention times, but due to instrument limitations, m/z > 1200 were not detected.

While there was no detectable EA present at the end of DVS addition at <7 °C, the conversion of oligomers of **1** to cyclic monomer **1** at 20 °C proceeded over the course of a day from 52% to >99% conversion (Figure 1). Additionally, the t = 0 NMR sample taken at the end of the DVS addition, which was far more dilute, was tracked over time to monitor the conversion of oligomers to **1** (Figure 1). Interestingly, the sample that was ∼30-fold more dilute (0.106 M (183 vol water)
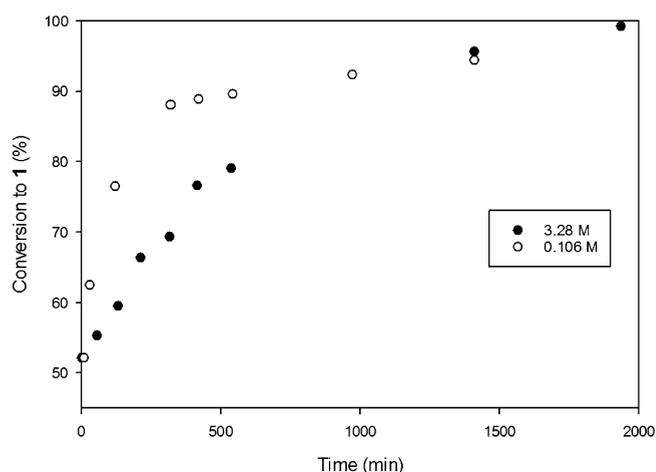
Figure 1. Conversion to **1** vs time post-DVS addition at 20 °C in a vial (3.28 M) and NMR tube (0.106 M).

vs 3.28 M (3 vol water) in EA proceeded ∼3-fold faster from ∼50−90% conversion. This behavior is consistent with a competition between an intramolecular reaction leading to **1** and an intermolecular reaction leading to oligomers **2**, **3**, **4**, **5**, etc.[12] As expected, the intermolecular process appears slower at lower concentrations, allowing the intramolecular process to dominate, leading to overall faster formation of **1** (Figure 1).

This transformation was also investigated computationally to understand the reversibility of the oligomer formation. DFT calculations (B3LYP, 6-31G*) revealed that formation of open-chain monomer **2** from EA and DVS is favorable by ∼4 kcal and that further conversion to product **1** is favored by an additional ∼19 kcal (Table 2). Open-chain dimer (**3**), trimer (**4**), tetramer (**5**), etc. are favored by ∼6 kcal relative to the starting materials and are viable intermediates. However, the oligomers are all much higher in energy than **1** (17−18 kcal), explaining why they convert to product, with sufficient time and temperature, in an irreversible manner. As experimental support for these calculations, the reaction enthalpy (EA + DVS to **1**) was predicted computationally as ΔH = −39.9 kcal, which aligns well with our previously measured value of ΔH = −33.9 kcal/mol.[13]

Table 2. Relative Energies of Intermediates en Route to 1

structure	calculated relative energy (ΔG, kcal)[a]
EA + DVS	0
2	−4.0
1	−23.4
3	−5.6
4	−5.8
5	−6.4

[a]Energies of oligomers are normalized based upon one EA and one DVS.

The experimental results demonstrating that intermolecular reaction of monomer **2** with EA or DVS leading to oligomers is competitive with intramolecular reaction of **2** to give product **1** were highly surprising. A possible explanation is that the geometric constraints of the intramolecular process make the transition state more strained. While conjugate addition to form open-chain species could be achieved through a six-membered ring chair transition state involving concerted transfer of the nitrogen to carbon and proton to oxygen, a similar intramolecular reaction involves a highly strained bicyclic [2.2.2] transition state structure, which would be higher in energy (Scheme 4).[14] While there have been previous reports on

Scheme 4. Proposed Transition State Structures for Intra- and Intermolecular Reaction of 2
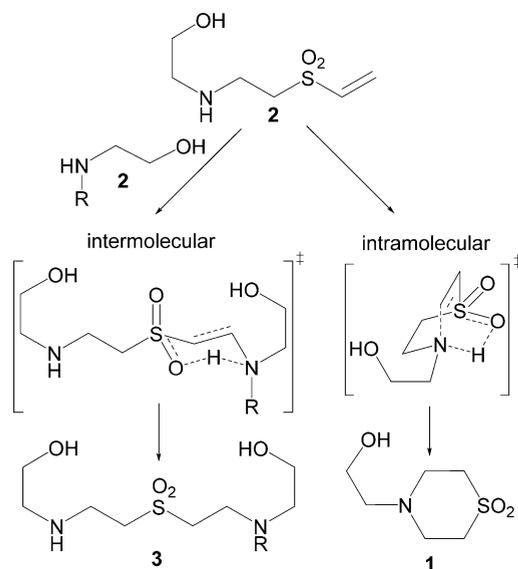
copolymerization of DVS with various amines or diamines, this is the first evidence for the reversibility of this process, and preferential monomer formation.[15]

With a firm understanding of the rapid rate of consumption of EA and the slower rate of conversion of intermediates (**2**–**5**, etc.) to **1**, we were ready to move ahead with development of a continuous process. As a next step, the reaction of DVS with EA was conducted on an intermediate scale in a 12 mL continuous reactor, which produced 150 g of **1** over ~1 h (Figure 2). This system was equipped with a DiComp IR flow cell, capable of monitoring the disappearance of DVS and the appearance of **1**. Strong IR bands at 1390 cm^{-1} (divinyl sulfone) and 1195 cm^{-1} (**1**) were readily monitored in this system, despite the use of water as a solvent, which can suppress IR signals even as a trace component. As shown in Figure 3, IR monitoring of this continuous process initially showed no signal when primed with only water and then showed a peak for divinylsufone shortly after pump B was started, followed by a peak for **1**, along with concomitant disappearance of divinyl sulfone, after pump A was started. IR showed that a steady state was established rapidly and maintained throughout, based on the consistent levels of DVS and **1**. After a 12 h age to promote oligomer conversion, the aqueous stream of **1** was analyzed by ^{1}H NMR and showed high purity of **1**.

Isolation of **1** was complicated by its extremely high water solubility (Table 3), leading us to study the impact of solvent, pH, and salt addition on an extractive workup. Among the water immiscible solvents examined, solubility of **1** was highest in DCM, but we also explored EtOAc as a greener alternative.[16] Using a solution of **1** in 2.7 vol of aqueous 25% K$_3$PO$_4$, extraction with 3 × 11 vol DCM resulted in 29%, 8%, and 2% of **1** remaining in the aqueous layer after each of the extractions. EtOAc was much less efficient, and extraction with 3 × 11 vol resulted in 69%, 52%, and 42% of **1** remaining in the aqueous layer after each of the extractions. Subsequent experiments with half as much DCM demonstrated that a pH of 10–11 (achieved by adding K$_2$CO$_3$ to a reaction stream) was optimal for extraction, and that the addition of KCl to make a 15 wt % aq solution gave ~10% better recovery per extraction than without salt.

With optimized workup conditions in hand, the end of reaction stream was concentrated by distilling half of the water, K$_2$CO$_3$ was charged to adjust the pH, and KCl was charged to adjust the ionic strength to minimize losses to the aqueous. The aqueous mixture was extracted with DCM, resulting in ~12% loss to the aqueous layer following the third extraction. The DCM was exchanged for MTBE through distillation, and the process stream was cooled to 0 °C to crystallize **1** in 74% yield. The yield and purity were comparable to material made previously through an otherwise identical small scale batch mode reaction using slow addition of DVS.
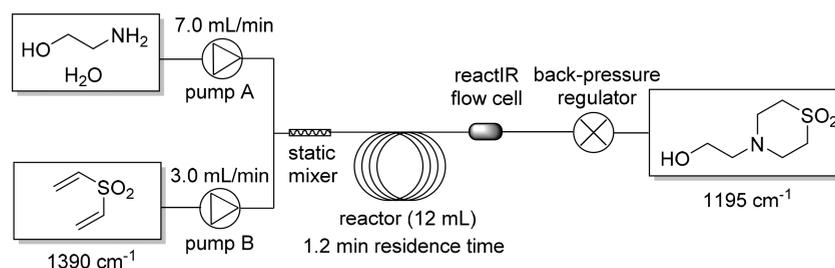
Figure 2. Equipment design for intermediate scale continuous process.
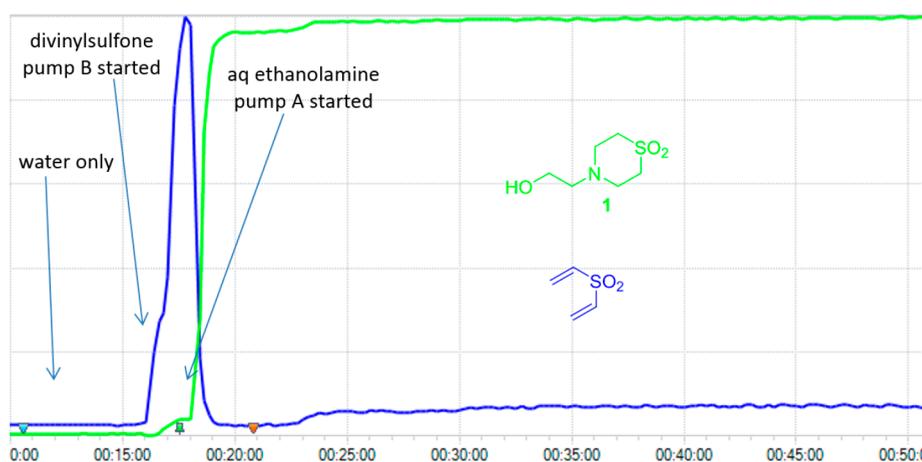
Figure 3. Monitoring of continuous process by ReactIR.

Table 3. Solubility of 1 in Water-Immiscible Solvents

solvent	solubility of 1 (mg/mL)
water	>1250
methyl acetate[a]	62.3
EtOAc	37.6
n-propyl acetate	18.9
isopropyl acetate	16.8
n-butyl acetate	13.8
isobutyl acetate	13.5
2-methyl THF	16.8
MTBE	3.6
DCM	96.0
DCE	71.7
toluene	3.4

[a]Forms a 25 wt % solution in water.

However, distillation of water from 6 to 3 volumes was an energy intensive and time-consuming operation, which was required to make the extraction into DCM efficient.[17] A modification was investigated whereby the continuous process could be run in 3 volumes of water (relative to EA), rather than the 6 volumes required for the batch reaction, to completely remove this distillation unit operation. While the estimated adiabatic temperature rise of 142 °C with this modification was deemed too high to be safe in batch mode, this would still be suitable for a continuous process where heat exchange with the cooling medium is very rapid.[5] A continuous reaction involving EA, 3 volumes water, and 1.04 equiv DVS was run on a 150 g scale and showed comparable behavior by ReactIR and a comparable reaction profile by ^{1}H NMR.

This process was next transferred to larger equipment for kg-scale production (Figure 4). To ensure safe, robust operation, the continuous reactor was equipped with (1) check valves to ensure back-mixing would not occur, (2) a ReactIR flow cell to monitor the steady state of the process in real time, (3) temperature and pressure monitors at several points throughout the equipment, (4) mechanical pressure relief valves set below the pressure rating of system, (5) a 30 psi automatic cutoff on the pumps to avoid overpressurization in the event of a clog, and (6) a 5 psi backpressure regulator to promote uniform flow.

The system was primed with water, before introducing neat DVS (22 mL/min) through one pump and an aq solution of EA (51 mL/min) through a second pump, giving a residence time of 1.6 min in the 110 mL reactor. Once the IR indicated that steady state had been reached, the flow path was diverted from waste to a jacketed 20 L reactor for collection, maintained at 20 °C. While a jacket for the continuous reactor was set at 20 °C, the temperature reached a steady state of ~40 °C immediately after the static mixer (~10 mL volume) due to
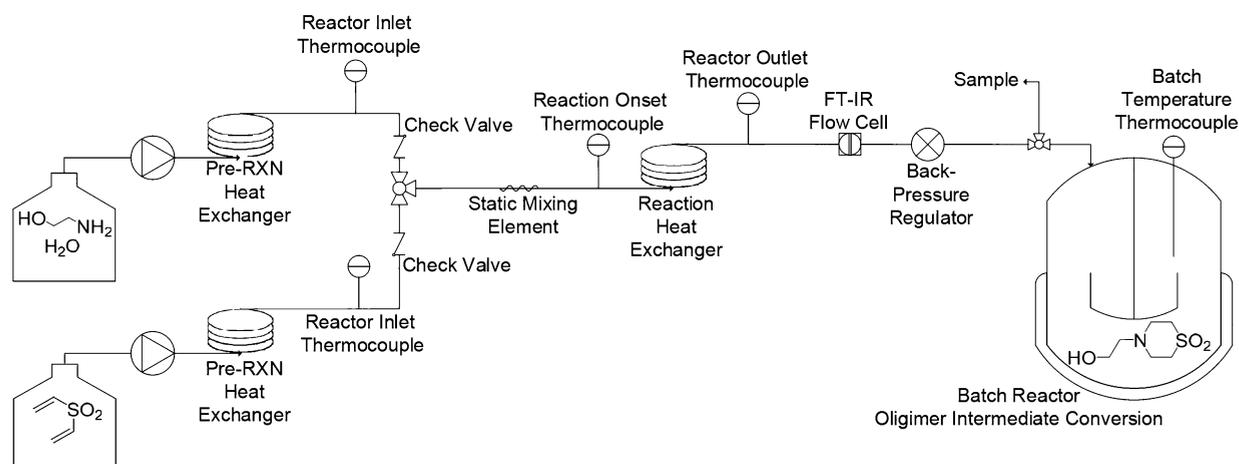
Figure 4. Equipment for plant scale production of 1.

the exothermicity of this process, although the stream had returned to 20 °C by the time it exited the continuous reactor.

Over the course of 2 h, DVS and an aqueous EA solution were pumped through the continuous reactor. The reaction mixture was collected in a 20 L reactor where it was aged for 12 h at 20 °C prior to workup and isolation, allowing for full conversion of intermediates to **1**. The solution was weighed and assayed by ^{1}H NMR showing a 98.5% in process yield of **1**.[18] K_2CO_3 and KCl were added to the reaction stream, which was extracted three times with DCM. After a solvent swap to MTBE and seeding with 0.5% **1**, a seed bed formed and the reaction mixture was cooled to −10 °C. The crystals were washed with MTBE and dried to give 2.45 kg of **1** in 71% yield. This white, crystalline powder had 100% potency and 99.8% purity by ^{1}H NMR. Although this was a short duration demonstration, it showed that by using very small equipment (110 mL continuous reactor) which maximizes heat transfer and minimizes safety hazards and plant footprint, **1** could be prepared at a rapid rate of ~1.6 kg/h, which could support any future material demands.

■ CONCLUSION

Our team has developed a safe, scalable, continuous manufacturing process for **1**, which circumvents the problem of a highly exothermic reaction not amenable to batch scale up. The highly concentrated reaction conditions allowed for a rapid, high-throughput process and a streamlined isolation procedure. Careful monitoring throughout production, including ReactIR for reaction progress, and temperature and pressure to ensure safe operation, were critical to the successful implementation of this process. Additionally, it was found that the initial product of EA and DVS is not **1** or even ring-opened intermediate **2**, but is rather a complex mixture of oligomers which eventually are transformed to **1**. NMR, MS, and computational methods were helpful in understanding the kinetics and thermodynamics of this fluxional system to ensure consistent product quality and yield.

■ EXPERIMENTAL SECTION

Preparation of 4-(2-Hydroxyethyl)thiomorpholine 1,1-Dioxide [CAS: 26475-62-7] (1) on Lab Scale. *Equipment Design.* Lab scale continuous flow reactions were performed using two HPLC pumps, a 2 mL (3-way, Uniqsis) glass chip for mixing, and a 10 mL (1/8 ″) Hastelloy coil. The glass chip and metal coil were submerged in a water batch held at 20 °C. A Mettler Toledo React IR instrument equipped with a DiComp in-line flow cell was used for real-time monitoring.

Process. The continuous reactor was primed with water, and then neat DVS (203.6 g, 173.3 mL, 1.03 equiv) was pumped through at a rate of 3.0 mL/min. Once the DVS signal was observed by ReactIR at the exit of the continuous reactor, an aqueous solution of EA (102.2 g in 303.2 mL of water) was introduced at 7.0 mL/min giving a ratio of 1.03:1 DVS/EA (residence time = 1.2 min). Once the DVS signal disappeared and the product reached a steady state, collection of the process stream in a reaction vessel was begun and continued for ~1 h. The process stream (554.1 g) was transferred to a 5 L reactor and, after stirring for 16 h, was diluted with DCM (1.40 L). Aqueous K_2CO_3 (11 mL, 20 wt % solution) was added to adjust the aqueous layer above pH 10. Solid KCl (101 g) was charged to the biphasic mixture which was stirred for 35 min until fully dissolved. The lower organic phase was reserved, and

the aqueous phase was extracted twice with DCM (1.40 L). The combined DCM extracts were concentrated to 700 mL and cooled to 30 °C. MTBE (2.25 L) was added over 2 h, with crystallization initiating after ~550 mL of MTBE had been introduced. The slurry was cooled to 0 °C over ~2 h and was aged for an additional 2 h at 0 °C before collecting the solid by filtration. The reactor was rinsed with 675 mL of MTBE at 0 °C, and this rinse was used to wash the filter cake. The cake was air-dried for 1 h and then was further dried in a vacuum chamber at 30 °C to yield 212 g of product (77.6% yield). ^{1}H NMR (500 MHz, D_2O) δ 3.64 (t, J = 5.9 Hz, 2H), 3.20 (d, J = 4.7 Hz, 4H), 3.08 (d, J = 4.7 Hz, 4H), 2.68 (t, J = 5.9 Hz, 2H).

Reaction of Ethanolamine and Divinylsulfone at Low Temperature and Conversion to 1. EA (400 mg) and water (1.2 mL) were combined in an 8 mL vial which was cooled in an ice bath. DVS (690 uL, 812 mg, 1.05 equiv) was added dropwise so that the temperature in the vial did not exceed 7 °C. After the addition was complete, the vial was transferred to a bath at 20 °C. Periodically (between 5 min and 32 h) 25 μL samples were diluted in 750 μL of D_2O and were analyzed by ^{1}H NMR within 5 min. The mixture of oligomers that formed was most consistent with trimer **4** by ^{1}H NMR, although LC-MS showed masses for monomer through hexamers. A sample taken 2 h after the temperature was increased to 20 °C (mixture with **1**): ^{1}H NMR (500 MHz, D_2O) δ 6.84 (dd, J = 16.0, 10.3 Hz, 1H), 6.37 (d, J = 16.5 Hz, 1H), 6.28 (d, J = 9.8 Hz, 1H), 3.62 (m, 6H), 3.45−3.38 (m, 10H), 3.04 (t, J = 6.3 Hz, 8H), 2.98 (t, J = 7.0 Hz, 2H), 2.64 (m, 6H). COSY (500 MHz, D_2O) δ 3.62−2.64, 3.42−2.98, 3.42−3.04. See Supporting Information for tentative assignments and comparison to **1**, EA, and DVS spectra. Since these samples could react on a relatively short time scale, they were not suitable for ^{13}C NMR analysis. LC-MS (ESI) method (Table 1): Ascentis Express C18, 2.7 μm, 4.6 mm × 50 mm, 1.5 mL/min, 220 nm, 40 °C, solvent A: 0.05% TFA in MeCN/water (5:95), solvent B: 0.05% TFA in MeCN/water (95:5), 0 to 10% B at 6 min, 10% to 100% B at 10 min.

Preparation of 4-(2-Hydroxyethyl)thiomorpholine 1,1-Dioxide [CAS: 26475-62-7] (1) on Plant Scale. *Equipment Design.* The plant scale continuous flow reaction was performed with an insulated tubing system composed of 1/4″ (0.035″ wall) Hastelloy C-276 Swagelok tubing. Each feed solution was filtered using Upchurch Scientific inlet solvent filters of 10 μm in porosity and was delivered to the continuous reactor via an Encynova Model 2−4 high precision liquid metering pump. Sentry tube-in-tube countercurrent heat exchangers (1/4″ inner tube diameter; 125 mL heat transfer volume) provided cooling to each feed stream prior to mixing as well as the resulting reaction mixture for additional residence time. The two feed streams combined in a jacketed 1/4″ Hastelloy C-276 Kenics KM static mixer (9.25″, 27 mixing elements). Cooling was provided using one portable air-cooled Budzar chiller unit; thus temperature control of the system was near isothermal. A Mettler Toledo Dicomp flow cell was installed at the continuous reactor outlet. Flow and pressure throughout the system was regulated using a downstream TESCOM 0−25 psi pressure regulator. The temperature was recorded with Omega Type T thermocouples in four locations; each stream prior to mixing (2), combined stream after mixing, and combined stream after residence time (reactor outlet). Endress and Hauser Promass 83A meters were used to record the mass flow exiting each feed pump.

Process. The temperature control was set to 10 °C, and the continuous reactor was flushed with water via both feed pumps until the process temperature stabilized. Neat DVS was pumped through the reactor to a waste container via pump B at a rate of 22 mL/min (9.96 M). Once the IR flow cell detected the presence of DVS, a 4.10 M EA solution (1496 g of EA in 4.5 L of water) was pumped via pump A at a rate of 51 mL/min (5% excess of DVS). After the IR flow cell detected the formation of product, the reaction stream was redirected from waste to an inerted 20 L glass reactor held at 25 °C. The flow rates remained constant throughout operation and resulted in a residence time of 1.6 min. The reaction stream was collected over ∼1.5 h, aged for 15 h at room temperature to allow complete conversion to **1**, and discharged into drums (6.90 kg). Analysis of the concentration of product in this stream by ^{1}H NMR vs an internal standard showed a 98.5% in-process yield. In a 50 L reactor, the reaction stream was combined with DCM (24.3 kg) and heated to 30 °C. Aqueous K_2CO_3 (178 g, 20 wt % solution) was added to adjust the aqueous layer to pH 11.3 (target pH > 10). Solid KCl (600 g) was charged to the biphasic mixture which was stirred for 2 h until fully dissolved. The lower organic phase was discharged to a drum, and the aqueous phase was extracted with DCM (2 × 24.0 kg). The combined DCM extracts were concentrated to ∼10 L through distillation where a KF of 450 ppm was achieved (target KF < 500 ppm). MTBE (3.90 kg) was added at a rate of ∼150 g/min followed by product seed (189g, 0.5 wt %). The remaining MTBE (18.8 kg) was added over 2 h, followed by cooling from 30 to −10 °C over 1.5 h. The product was isolated in a Buchner funnel and was washed with MTBE (6.86 kg). The material was tray dried at 40 °C and ∼100 mbar over 24 h to give **1** as a white crystalline solid (2.45 kg, 71% yield). The potency by QNMR was 100%, and the purity by NMR was >99.8%. Mp = 75.2 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.51 (t, J = 4.0 Hz, 1H), 3.52−3.47 (m, 2H), 3.07−3.04 (m, 4H), 2.95−2.93 (m, 4H), 2.57 (t, J = 4.0 Hz, 2H). ^{13}C {^{1}H} NMR (100 MHz, DMSO-d_6) δ 58.77, 57.73, 50.65, 50.32. HRMS (ESI-MS) calcd for $C_6H_{14}NO_3S$: 180.0694 (M + H)$^+$], found 180.0698.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.8b00100.

Spectroscopic data and computational details (PDF)

■ AUTHOR INFORMATION

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Notes
The authors declare no competing financial interest.

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(2) Ford-Moore, A. H.; Lidstone, A. G.; Waters, W. A. Syntheses of some β-Chlorinated Amines. *J. Chem. Soc.* **1946**, *0*, 819−820.

(3) The T_{ad} was measured by heat flow calorimetry on an RC1 with 6 L of water per kg of ethanolamine.

(4) With a large T_{AD}, there is a risk of a batch reaction mixture overpressuring or thermal decomposition.

(5) Divinyl sulfone exhibits strongly exothermic decomposition behavior with an onset of 160 °C based on DSC with a predicted adiabatic decomposition temperature in 24 (ADT24) of 120 °C. An advanced reactive system screening tool (ARSST) was used to scan for thermal decomposition of the reaction mixture, but we did not see any decomposition up to 150 °C at the end of the scan.

(6) Divinylsulfone has been classified as an acute toxin hazardous chemical by the European Chemicals Agency: https://echa.europa.eu/substance-information/-/substanceinfo/100.000.962. Divinylsulfone has been deemed a hypertoxic chemical in China based on the following numeric cut-off criteria: Oral LD50 ≤ 5mg/kg bodyweight, or Dermal LD50 ≤ 50mg/kg bodyweight, or Inhalation LC50 ≤ 0.5 mg/L (vapor): http://www.chinasafety.gov.cn/newpage/Contents/Channel_5330/2015/0309/247023/content_247023.htm.

(7) Flow can minimize exposure to toxic reagents by limiting the volume of reactor spills/leaks and avoiding over-pressurization events. For a review of handling hazardous reagents in flow, see: Movsisyan, M.; Delbeke, E. I. P.; Berton, J. K. E. T; Battilocchio, C.; Ley, S. V.; Stevens, C. V. Taming Hazardous Chemistry by Continuous Flow Technology. *Chem. Soc. Rev.* **2016**, *45*, 4892−4928.

(8) When ethanolamine and divinyl sulfone were combined at 1/40th of the reaction concentration, complete consumption was observed within 2 min, verifying the rapid rate for this bimolecular reaction.

(9) While divinylsulfone and **1** could be observed by HPLC, the broad peak shapes and inconsistent retention times made NMR a superior method for analysis.

(10) See Supporting Information for interpretation of ^{1}H NMR

(11) Product **1** has a much weaker chromaphore than oligomers of **1** bearing a vinylsulfone moiety, resulting in the low UV response.

(12) The faster conversion to **1** under more dilute conditions could also be explained by a change in the solvent composition from 50% water to 99% water, in accordance with a change in the dielectric constant of the system.

(13) This difference between the experimental and computational prediction of Δ*H* could be explained by aqueous solvation which was not taken into account in the gas phase calculations.

(14) Using computations we were not able to identify a transition state for intramolecular cyclization of **2** to **1**.

(15) (a) Gao, C.; Yan, D.; Zhu, X.; Huang, W. Preparation of water-soluble hperbranched poly(sulfone-amine)s by polyaddition to N-ethylethylenediamine to divinylsulfone. *Polymer* **2001**, *42*, 7603−7610. (b) Gao, C.; Yan, D. Polyaddition of B2 and BB′2 Type Monomers to A2 Type Monomer. 1. Synthesis of Highly Branched Copoly(sulfone-amine)s. *Macromolecules* **2001**, *34*, 156−161. (c) Yan, D.; Gao, C. Hyperbranched Polymers Made from A2 and BB′2 Type Monomers. 1. Polyaddition of 1-(2-Aminoethyl)piperazine to Divinyl Sulfone. *Macromolecules* **2000**, *33*, 7693−7699.

(16) Although the solubility was higher in methyl acetate, it was not investigated for development due to its high water solubility and susceptibility to hydrolysis.

(17) The reaction was also investigated in alcoholic solvents (MeOH, IPA, *n*-BuOH), which gave fast consumption of the ethanolamine, but much slower conversion of oligomers to **1**.

(18) The yield was based on the mass of reaction stream collected and excluded any ethanolamine stream sent to waste prior to achieving steady state. For a larger scale, a several hour production run, any losses during this startup transition would be negligible in the context of the entire manufacture.