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Development of Safe, Scalable Nitric Acid Oxidation Using a Catalytic Amount of $NaNO_2$ for 3-Bromo-2,2-bis(bromomethyl)propanoic Acid: An Intermediate of S-013420

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S *Supporting Information*

ABSTRACT: A safe, scalable process was developed for nitric acid oxidation of 3-bromo-2,2-bis(bromomethyl)propan-1-ol (**2**) to give 3-bromo-2,2-bis(bromomethyl)propanoic acid (**3**), an intermediate in the synthesis of S-013420 (**1**). The key points are the use of a catalytic amount of $NaNO_2$ and addition of the starting material in portions. We achieved 3,000 L scale pilot production.

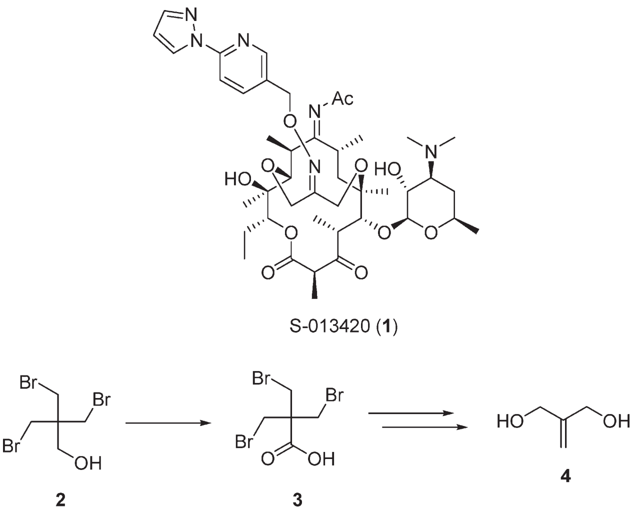
INTRODUCTION

Nitric acid is a strong oxidant that has been widely used for a long time.[1] However, other mild oxidants such as Dess−Martin periodinane,[2] 2,2,6,6-tetramethylpiperidine-1-oxyl (TEMPO),[3] 2-iodoxybenzoic acid (IBX),[4] $RuCl_3$−$NaIO_4$,[5] and tetrapropyl ammonium perruthenate (TPAP)[6] have been used more often than nitric acid because the strong acidic nature of nitric acid causes decomposition of unstable substrates and sometimes produces nitro aromatic compounds. In addition, oxidizing specific parts of compounds with nitric acid is difficult, and oxidation using nitric acid has sometimes resulted in a thermal runaway reaction.[7] However, if the oxidation product is stable in strong acid and the reaction heat and gases can be safely controlled, nitric acid oxidation can be valuable, especially in the chemical industry, because nitric acid is inexpensive and has no toxic potential. Such an oxidation procedure would be simple, easy, and environmentally friendly because the side products are gases such as oxides of nitrogen. In addition, nitric acid oxidation is a clean direct method of converting alcohols to carboxylic acids in contrast to other methods such as Jones oxidation (CrO_3, H_2SO_4, acetone)[8] and $KMnO_4$ oxidation,[9] which require very toxic reagents and can cause environment pollution. For these reasons, we chose nitric acid as an oxidant for the process of manufacturing the starting material methylene diol (**4**) for S-013420 (**1**), a novel bicyclolide (bridged bicyclic macrolide).[10] The route to intermediate **4** is illustrated in Scheme 1. The reaction conditions of the oxidation (**2** → **3**) were optimized, and a detailed safety evaluation study was conducted. The pilot manufacturing was successful on a 3,000 L scale. Here we report the details of safe, practical oxidation with nitric acid for scale-up manufacturing and also discuss the reaction mechanism.

RESULTS AND DISCUSSION

Preliminary Experimental Study and Optimization of Nitric Acid Oxidation. At first, oxidation of **2** using 68% nitric acid was carried out at 90 °C and gave the desired product **3** in 80% yield. However, there were three issues for scale-up production: (1) there is an induction period before the reaction starts, (2) the reaction mixture has two phases from the beginning to the end, and (3) the generation of reaction heat and gases cannot be controlled as it is a full batch reaction. To overcome these problems, starting material **2** was dissolved in acetic acid, and this solution was added to 68% nitric acid containing a catalytic amount of $NaNO_2$ in accordance with the literature.[1f] As a result, the induction period was shortened, and the generation of reaction heat and gases also seemed to be controllable.

Scheme 1



Safety Evaluation of Nitric Acid Oxidation. The calories and the generation of NO_x gases were measured by RC1e as shown in Figure 1 and Table 1. The solution of starting material **2** in acetic acid (1 vol) was added to a mixture of 68% nitric acid (8.0 equiv) and $NaNO_2$ (1.0 mol %) dropwise over 2 h at 65 °C. The

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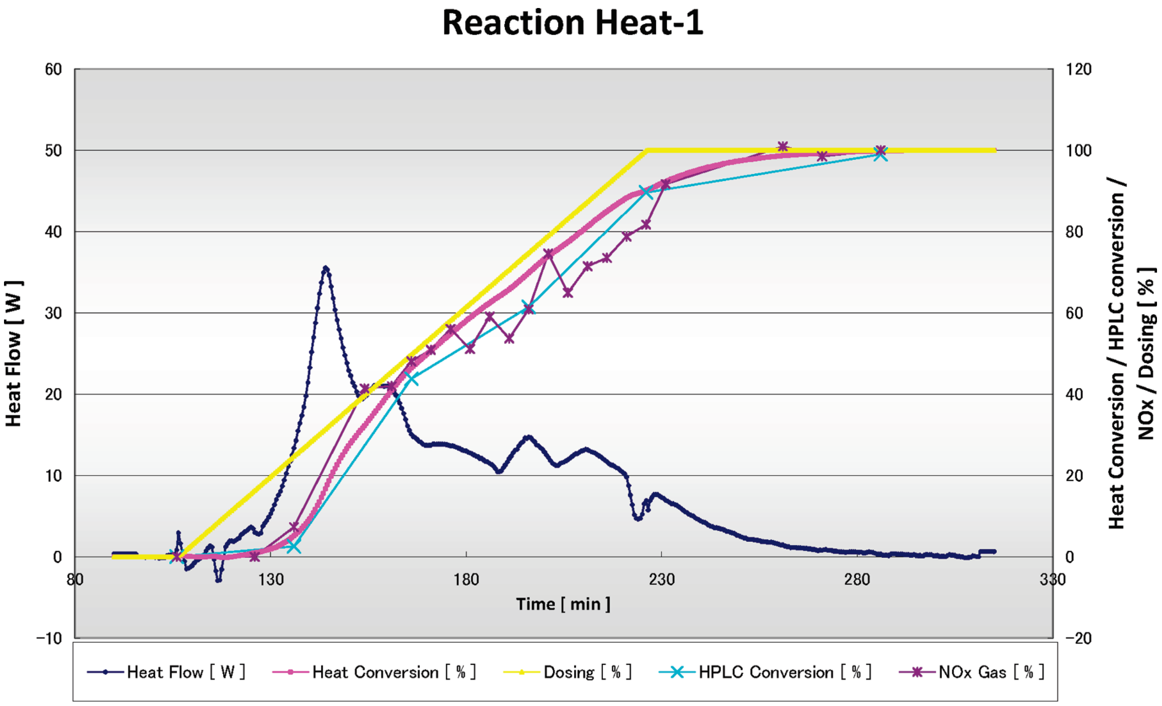

Figure 1. Reaction heat and gas generation 1.

Table 1. Result of RC1e Experiment 1

ΔH_{react} (kJ/mol)[a]	dropwise addition time (min)[b]	specific heat of reaction mass (J/(g·K))	ΔT_{ad} (K)
216.0	120	2.60	113.8

[a] Based on charged **2**. [b] Dropwise addition of a solution of **2** in acetic acid.

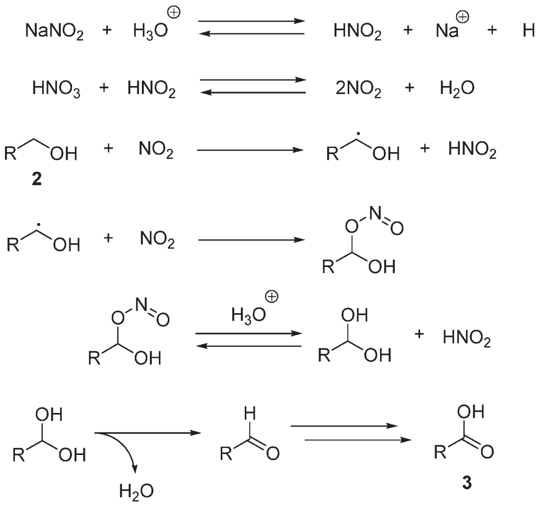

Figure 2. Plausible reaction mechanism.

total reaction calorie level was 216.0 kJ/mol, and the adiabatic temperature rise (ΔT_{ad1}) was 113.8 K. The instantaneous maximum reaction heat was 35 W when 33% of starting material **2** was added. The maximum temperature of the synthetic reaction (MTSR) by this ΔT_{ad1} is 178.8 °C. As the accumulation of the reaction heat and NO_x gases generation were observed in the early stages (when 25% of starting material **2** in acetic acid was added, only 14% heat and 7% gases generation were observed), further investigation was necessary to ensure safety.

Consideration of the Reaction Mechanism of Nitric Acid Oxidation. The following reaction mechanism is proposed in the literature[1a] as shown in Figure 2. First, $NaNO_2$ is converted to HNO_2 in the acidic condition and HNO_2 reacts with nitric acid to form NO_2. Alcohol reacts with NO_2 and becomes an alkyl radical, which is oxidized by NO_2 to form alkyl nitrite (R-CH(OH)-O=N-O). This alkyl nitrite reacts with nitric acid in the acidic condition and becomes diol, which is immediately converted to aldehyde. Further oxidation by nitric acid leads to carboxylic acid **3**. According to this mechanism, the rate of reaction depends on the concentration of NO_2, and thus the initial rate of the reaction in the previous condition is slow because only a small amount of NO_2 is present in the initial reaction mixture. When a small portion of starting material **2** is added as an initiator, enough NO_2 would be generated and the rate of the reaction would be greater from the beginning. On the basis of this idea, further investigation was conducted.

Investigation for Safer Nitric Acid Oxidation and Safety Evaluation. The amount of the starting material for the initiation was set at 10% because the adiabatic temperature rise calculated from previous data was approximately 11 K, and MTSR would be 76.0 °C, which is lower than the boiling point of the solvents (nitric acid 83 °C, water 100 °C, and acetic acid 118 °C). To initiate the reaction, 10% starting material **2** in acetic acid was added, and after using HPLC to confirm that all of the starting material had been consumed, the remaining 90% of starting material **2** in acetic acid was added dropwise over 3 h. The RC1e result is shown in Figure 3 and Table 2. The adiabatic temperature rise (ΔT_{ad2}) of the initiation by dosing 10% starting material **2** was 10.0 K, and ΔT_{ad3} of the reaction by dosing the

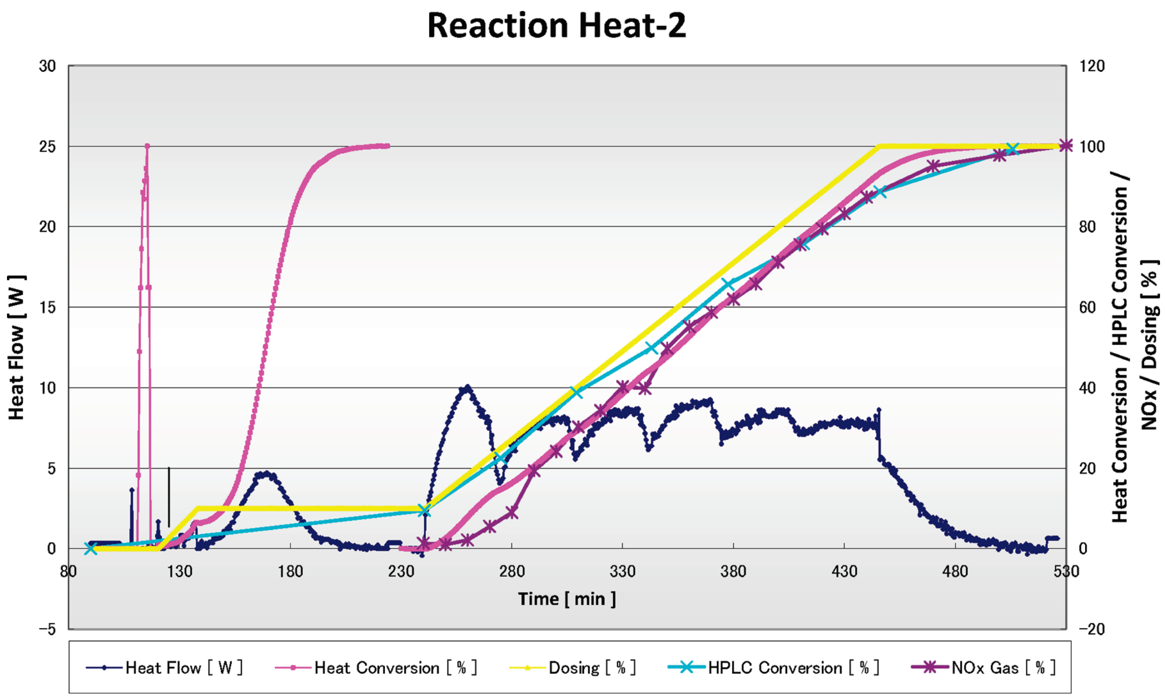

Figure 3. Reaction heat and gas generation 2.

Table 2. Result of RC1e Experiment 2

	ΔH_{react} (kJ/mol)[a]	dropwise addition time (min)[b]	specific heat of reaction mass (J/(g·K))	ΔT_{ad} (K)
10% **2** and acetic acid	18.3	18	2.51	10.0
90% **2** and acetic acid	218.3	180	2.50	109.6

[a] Based on charged **2**. [b] Dropwise addition of a solution of **2** in acetic acid.

Table 3. Results of DSC Experiment[a]

	T_{onset} (°C)	enthalpy (J/g)	T_{onset} at mp (°C)	enthalpy at mp (J/g)
alcohol **2**			92.52	−58.46
alcohol **2** in aceteic acid[b]	249.84	23.57		
carboxylic acid **3**	269.83	22.61	120.13	−35.91

[a] Heating rate; 10 °C/min. [b] Alcohol **2**/acetic acid = 1:1 (w/w).

remaining 90% of starting material **2** was 109.6 K. The instantaneous maximum reaction heat was 10 W, and the reaction heat could be safely controlled by the dropwise addition of the remaining 90% reactant,[11] which also controlled the NO_x gases generation from the early period as expected. The exothermic heat of starting material **2**, a solution of **2** in acetic acid, and product **3** was measured by DSC. The results are summarized at Table 3. The significant exothermic peak was not observed at all samples. This procedure was much safer than the previous one and was adapted for pilot plant manufacturing.

Application in a Manufacturing Facility. Pilot manufacturing using this oxidation was carried out with a 3,000 L glass-lined reactor. Hydrolysis of NO_x gases was carried out in an alkali scrubber. At 20 min after addition of 10% of the starting material in one portion as an initiator, an increase in temperature of approximately 2 K was observed, and in-process testing by HPLC[12] showed that all of starting material **2** had been consumed. The reaction heat and the gas generation were well controlled by gradual addition of the remaining starting material **2** from the beginning to the end, and no leakage of acidic gases from the alkali scrubber was observed. The purity of the obtained crystals from the manufacturing run was comparable to that of the lab run.

■ CONCLUSION

Safe, scalable nitric acid oxidation using a catalytic amount of $NaNO_2$ was applied to pilot manufacturing of 3-bromo-2,2-bis(bromomethyl)propanoic acid (**3**), which is an intermediate of S-013420 (**1**). Initiation was successfully conducted with 10% starting material, and the reaction heat and gas generation could be successfully controlled. This led to successful scale-up manufacturing on a scale of 425 kg.

EXPERIMENTAL SECTION

NMR spectra were measured on a Varian MERCURY-300VX. High performance liquid chromatographic (HPLC) analysis was carried out using a Shimadzu LC-10ADVP. DSC measurements were conducted on a METTLER TOLEDO SDC822e.

Procedure for Manufacturing Acid 3 in a Pilot Plant. $NaNO_2$ (0.9 kg, 13 mol) was dissolved in 68% nitric acid (992.6 kg, 10712 mol), and the mixture was heated to 65 °C. Alcohol **2** (425.0 kg, 1308 mol) was dissolved in acetic acid (425.0 kg), and 10% of this solution was added to the nitric acid solution at 65 °C. After the complete consumption of alcohol **2** had been confirmed by HPLC, the remaining 90% of alcohol **2** in acetic acid was added dropwise over 3 h, and the whole mixture was stirred for 1 h. After completion of the reaction had been confirmed by HPLC, the reaction mixture was cooled to 32 °C, and the product was observed to precipitate. The mixture was stirred for 1 h at the same temperature. After 1148.0 kg of water (2.7 vol) was added, the slurry was aged for 3 h, cooled to 5 °C, and stirred for 1 h at the same temperature. The crystals were filtrated on a Nutsche plate filter, washed with water (1148.0 kg, 2.7 vol), and dried using a double-cone dryer under reduced pressure at 55 °C. By this procedure, 394.1 kg of acid **3** was obtained (isolated yield 88.9%). Mp 98−99 °C, lit.[12] mp 98−100; ^1H NMR (300 MHz, $CDCl_3$) δ 3.76 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 32.50, 53.24, 174.29.

ASSOCIATED CONTENT

Ⓢ **Supporting Information.** Copies of ^1H NMR and ^{13}C NMR of compound **3**; copies of RC1e, DSC, and HPLC results. This material is available free of charge via the Internet at http://pubs.acs.org.

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NOTE ADDED AFTER ASAP PUBLICATION

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