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Risk Assessment and Safety Evaluation Study for Ozonolysis of β-Pinene: Raw Material of a Novel Prostaglandin D_2 Receptor Antagonist S-5751

Takemasa Hida,[*,†] Junko Kikuchi,[‡] Makoto Kakinuma,[§] and Hideo Nogusa[§]

Shanghai Office, Shionogi & Co., Ltd., 306A, 3F, Building A, Far East International Plaza, No. 319, Xianxia Road, Shanghai 200051, China, Discovery Research Laboratories, Shionogi & Co., Ltd., 12-4, Sagisu 5-chome, Fukushima-ku, Osaka 553-0002, Japan, and CMC Development Laboratories, Shionogi & Co., Ltd., 1-3, Kuise Terajima 2-chome, Amagasaki, Hyogo 660-0813, Japan

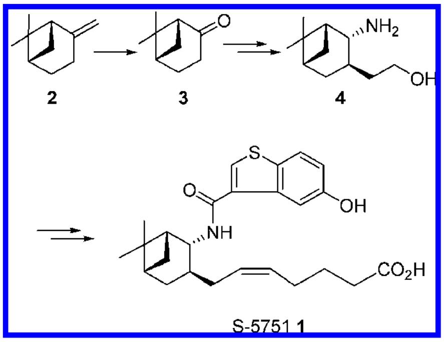
Abstract:

Safety evaluation for ozonolysis of β-pinene was conducted using DSC, ARC, and RC1e. ARC measurement showed that the concentration of the ozonized mixture affects its thermal stability. The sample at a high concentration of 1.83 mol/L was very unstable even at room temperature and decomposed rapidly. ADT_{24} of the diluted sample of 0.73 mol/L was 28.2 °C. Although reductive decomposition of the ozonized mixture at extremely low temperature is very dangerous because of accumulation of the heat of reaction, its process temperature was validated to not exceed the ADT_{24}. As a result, pilot manufacturing on a 300-L reactor scale could be achieved.

Introduction

Since Schönbein first studied ozonolysis in 1855,[1] this reaction has been applied to many types of industrial production,[2] for example, for the preparation of antibiotics such as ceftibuten and cefaclor.[3,4] Ozonolysis is a useful reaction for obtaining carbonyl compounds directly from olefins, and ozone is a very "green" oxidant because it only produces oxygen as a coproduct after the reaction. However, ozonolysis is known to be a very dangerous reaction which may cause explosions. Recently, microreactor systems have been used for kilogram-scale synthesis,[5] but detailed safety evaluation study and risk assessment of ozonolysis are needed for practical industrial manufacturing.

Scheme 1. **New synthetic route to S-5751 1 from β-pinene 2**



(+)-Nopinone **3** is a raw material of the prostaglandin D_2 (PGD_2) receptor antagonist S-5751 **1**, which was discovered at Shionogi Research Laboratories.[6,7] Several synthetic methods have been reported for obtaining its key intermediate.[8−10] A new synthetic route from **3** to (+)-2-((1*R*,2*R*,3*R*,5*S*)-2-amino-6,6-dimethylbicyclo[3.1.1]hept-3-yl)-ethanol (**4**), which is one of the key intermediates of S-5751, was reported by the Shionogi group.[10] To obtain **3**, ozonolysis of β-pinene **2** is necessary. Although a procedure for obtaining **3** from **2** using ozonolysis has been reported by Grimshaw et al.,[11] a detailed safety evaluation study is necessary for scale-up manufacturing of **3**. Here we describe a risk assessment and detailed safety evaluation study of ozonolysis and present a case of practical application for scale-up ozonolysis.

Results & Discussion

Identification of Products from Ozonolysis and Their Evaluation Using CHETAH. Reaction products were determined by NMR of the reaction mixture. The reaction mechanism by Criegee[12] is outlined as follows (Scheme 2). In the first step, ozone and **2** made the 1,2,3-trioxolane structure (primary ozonide **5**). In the second step, **5** underwent heterolysis to give a zwitterion (**6** or **7**) and a carbonyl compound (**3** or formaldehyde **8**). In the final step, the zwitterion combined with the carbonyl compound to give normal ozonide **9**. However this ozonolysis was carried out in methanol. In a protonic solvent, here methanol, **7** can be easily diverted to **10** instead

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[*] To whom correspondence should be addressed. Fax: 86-21-6235-1311. Telephone: 86-21-6235-1311. E-mail: takemasa.hida@shionogi.co.jp.

[†] Shanghai Office, Shionogi & Co., Ltd.

[‡] Discovery Research Laboratories, Shionogi & Co., Ltd.

[§] CMC Development Laboratories, Shionogi & Co., Ltd.

(1) Schönbein, C. F. *J. Pract. Chem.* **1855**, *66*, 282.

(2) Van Ornum, S. G.; Champeau, R. M.; Pariza, R. *Chem. Rev.* **2006**, *106*, 2990.

(3) Yoshioka, M. *Pure Appl. Chem.* **1987**, *59*, 1041.

(4) Bernasconi, E.; Lee, J.; Sogli, L.; Walker, D. *Org. Process Res. Dev.* **2002**, *6*, 169.

(5) Hübner, S.; Bentrup, U.; Budde, U.; Lovis, K.; Dietrich, T.; Freitag, A.; Küpper, L.; Jähnisch, K. *Org. Process Res. Dev.* **2009**, *13*, 952.

(6) Arimura, A.; Yasui, K.; Kishino, J.; Asanuma, F.; Hasegawa, H.; Kakudo, S.; Ohtani, M.; Arita, H. *J. Pharmacol. Exp. Ther.* **2001**, *298*, 411.

(7) Mitsumori, S.; Tsuri, T.; Honma, T.; Hiramatsu, Y.; Okada, T.; Hashizume, H.; Kida, S.; Inagaki, M.; Arimura, A.; Yasui, K.; Asanuma, F.; Kishino, J.; Ohtani, M. *J. Med. Chem.* **2003**, *46*, 2446.

(8) (a) Campos, K. R.; Lee, S.; Journet, M.; Kowal, J. J.; Cai, D.; Larsen, R. D.; Reider, P. J. *Tetrahedron Lett.* **2002**, *43*, 6957. (b) Campos, K. R.; Journet, M.; Lee, S.; Cai, D.; Kowal, J. J.; Lee, S.; Larsen, R. D.; Reider, P. J. *J. Org. Chem.* **2003**, *68*, 2338.

(9) Jennequin, T.; Labat, S.; Toupet, L.; Caille, J. C.; Mauduit, M. *Synlett* **2008**, *11*, 1669.

(10) Hida, T.; Mitsumori, S.; Honma, T.; Hiramatsu, Y.; Hashizume, H.; Okada, T.; Kakinuma, M.; Kawata, K.; Oda, K.; Hasegawa, A.; Masui, T.; Nogusa, H. *Org. Process Res. Dev.* **2009**, *13*, 1413.

(11) Grimshaw, J.; Grimshaw, J. T.; Junejia, H. R. *J. Chem. Soc. Perkin 1* **1972**, *50*.

(12) Criegee, R.; Scröder, G. *Chem. Ber.* **1960**, *93*, 689.

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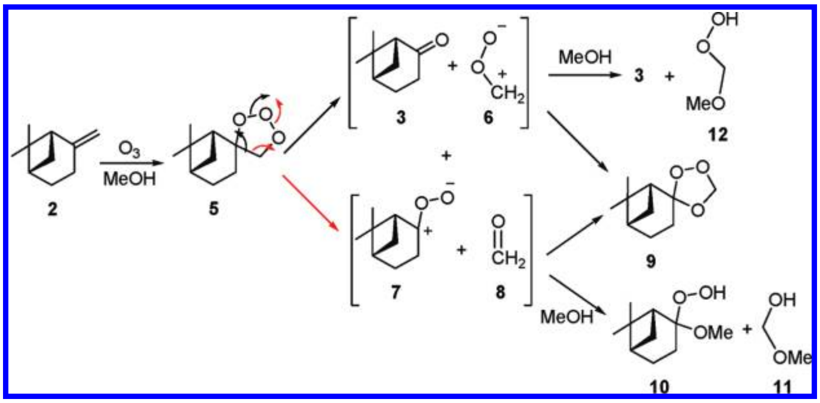
Scheme 2. **Reaction mechanism and products on the ozonolysis of *β*-pinene 2**



of **9**.[13] According to this mechanism, zwitterion **7** might dimerize to **13** or polymerize to **14** (Figure 1), both of which seem to be difficult to reduce, but these compounds were not detected in the NMR chart. The major products were methoxy hydroperoxide **10** and **11**, and (+)-nopinone **3** and ozonide **9** were detected as minor products. During the NMR measurement, **10** was found to be very unstable to heat and was decomposed to **3** even at room temperature overnight (Figure 2). On the other hand, **9** was difficult to decompose to **3**. These results mean that the reaction is fraught with the danger of turning into an explosive decomposition by **10** under adiabatic conditions.

The potential explosive risks of **9** and **10** were assessed by theoretical calculation using CHETAH software (Table 1). From the results, although $|\Delta H_c - \Delta H_d|$ of both **9** and **10** are not so high, both compounds are explosive. The ΔH_d's of both compounds are comparatively large,[14] and they should be treated carefully.

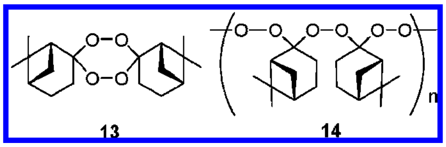


Figure 1. **Putative dimer and polymer.**

Thermal Screening with DSC and ARC. Using DSC, the exothermal energy value and onset temperature of the ozonized mixture in methanol, which is charged on 1.83 mol/L of **2** (∼29 w/w% of **10**), were measured using both gold and SUS cells (Table 2 and Figure 3). The exothermal energy and peak shape are similar, regardless of the material of cell. Thus, the SUS reactor can also be used for actual manufacturing. Although DSC shows the onset point at over 70 °C, the actual temperature rise of the exothermal peak starts from 50 °C. The exothermic curve is sharp, and the decomposition seems to proceed explosively. These data indicated that the ozonized mixture should be treated at very low temperature. We concluded that such an extremely unstable compound should be investigated in more detail; therefore, we carried out ARC measurements.

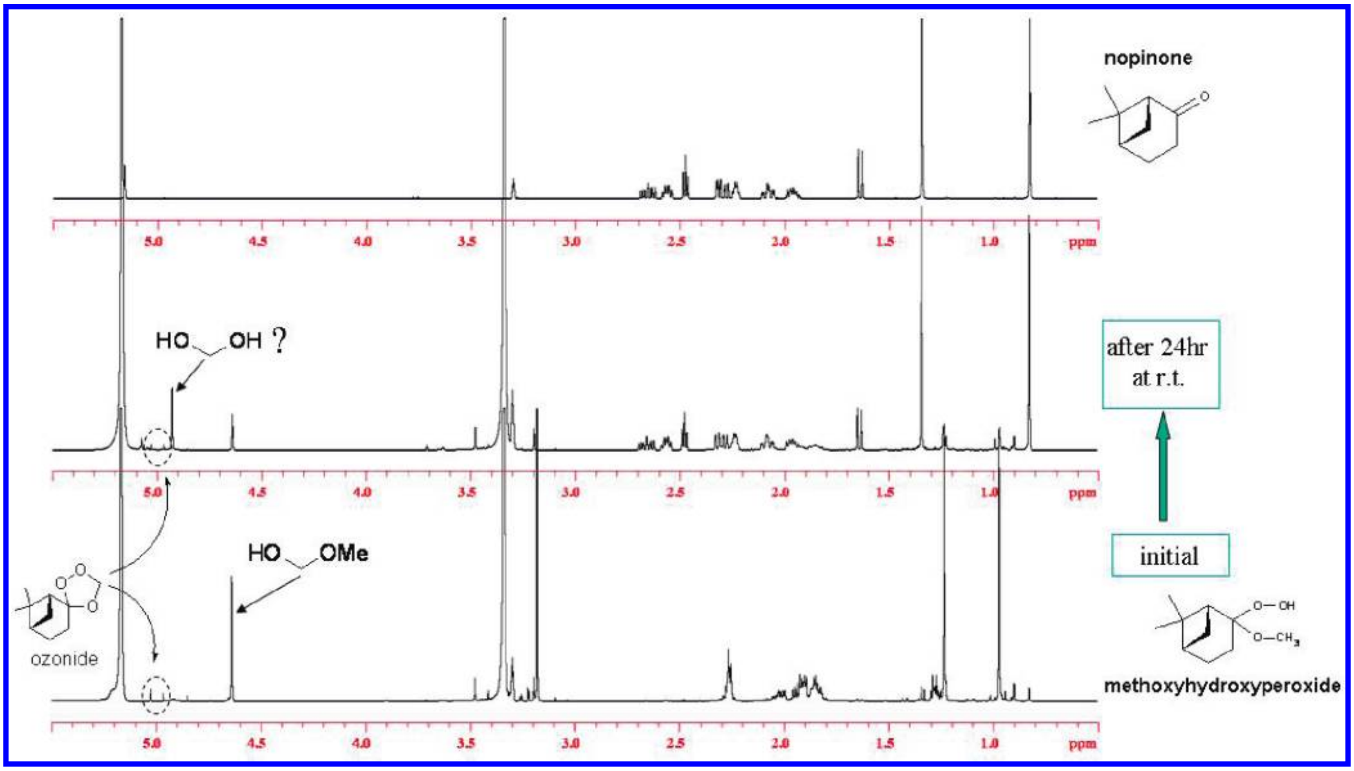


Figure 2. **NMR of ozonized mixture and its transformation at room temperature for overnight.**

Table 1. Results of CHETAH

compound	$\Delta H_c{}^a$ kJ/g	$\Delta H_d{}^b$ kJ/g	$\lvert\Delta H_c - \Delta H_d\rvert$ kJ/g	oxygen balance gO_2/100 g	overall energy release potential	net plosive density
9	–29.472	–2.608 MEDIUM	27.725 LOW	–223.346 MEDIUM	–0.337 HIGH	0.277 PLOSIVE
10	–30.322	–2.566 MEDIUM	26.917 LOW	–217.106 MEDIUM	–0.348 HIGH	0.275 PLOSIVE

[a] Fuel value. [b] Maximum heat of decomposition.

Table 2. DSC data of ozonized mixture[a]

material of cell	onset (°C)	peak top (°C)	energy ΔH (J/g)
gold	71	107	519
SUS	81	105	523

[a] Using ozonized mixture (concentration substrate/methanol: 1.83 mol/L of **10**). Scanning ratio is 10 K/min. Range of scanning temperature dis from −25 to 350 °C.

The ozonized mixture, the concentration of which is the same as that of the DSC sample, ∼29 w/w% of **10**, was measured by ARC (Figure 4). It was found to be too unstable even at room temperature to detect the onset temperature of self-heating. The rate of self-decomposition was fast and its adiabatic temperature was over 108.70 °C (after φ correction).[15] Therefore, a diluted ozonized mixture, 0.73 mol/L (∼14 w/w% of **10**), was prepared and subjected to measurement (Figure 5). It showed an onset temperature of self-heating of 42.09 °C, and thus the ADT_{24} was calculated to be 28.2 °C after φ correction and extrapolation.[16] Self-heating was raised to 65.42 °C, and thus the adiabatic temperature rise was calculated to be 44.39 °C from the φ correction.

The process temperature of ozonolysis and reductive decomposition should be controlled at below ADT_{24}. Next, we measured the heat of reaction and set the upper limits for the process temperature.

The ARC measurements yielded experimental results showing that the stability of the ozonized mixture is closely related to the reaction concentration. The exothermic curve of 1.83 mol/L differs from that of 0.73 mol/L. In view of the ARC chart of 1.83 mol/L (Figure 4), in which the pressure curve is a single one while the exothermic curve has two more slopes, the decomposition seems to proceed by interaction with two molecules of **10** but not with methanol. In 0.73 mol/L of the ozonized mixture, the decomposition seems to proceed with one molecule of **10** itself because the exothermic curve is only a slope (Figure 5). Thus, dilution of the product is necessary to stabilize the product.

Heat of Reaction (RC1e). The heat of reaction for ozonolysis of **2** was measured by RC1e (Table 3 and Figure 6). It is a very large value of 498.95 kJ/mol but can be controlled by the flow rate of O_3/O_2. In addition to controlling the heat of ozonolysis, the reaction temperature must be kept low from the viewpoint of assuring safety. The ozonolysis is carried out under an oxygen atmosphere, and the concentration of methanol in vapor should be controlled to below the lower explosive limit in oxygen.

Reductive decomposition of the ozonized mixture using trimethyl phosphite was carried out to obtain **3**, and the heat of reaction was measured at −25 °C (Table 4 and Figure 7). It was found that the accumulation of heat on dropwise addition of 1.0 equiv of trimethyl phosphite is over 33%. Then the heat of reaction was measured at −10 °C; however, the heat of reaction at dropwise addition of 1.0 equiv of trimethyl phosphite still accumulated 25% (Table 4 and Figure 6). Although the ozonized mixture is very unstable to heat and the upper process temperature should be controlled at below ADT_{24}, reductive treatment should not be carried out at extremely low temperatures. The control of reductive decomposition seems to be the most important point for safety

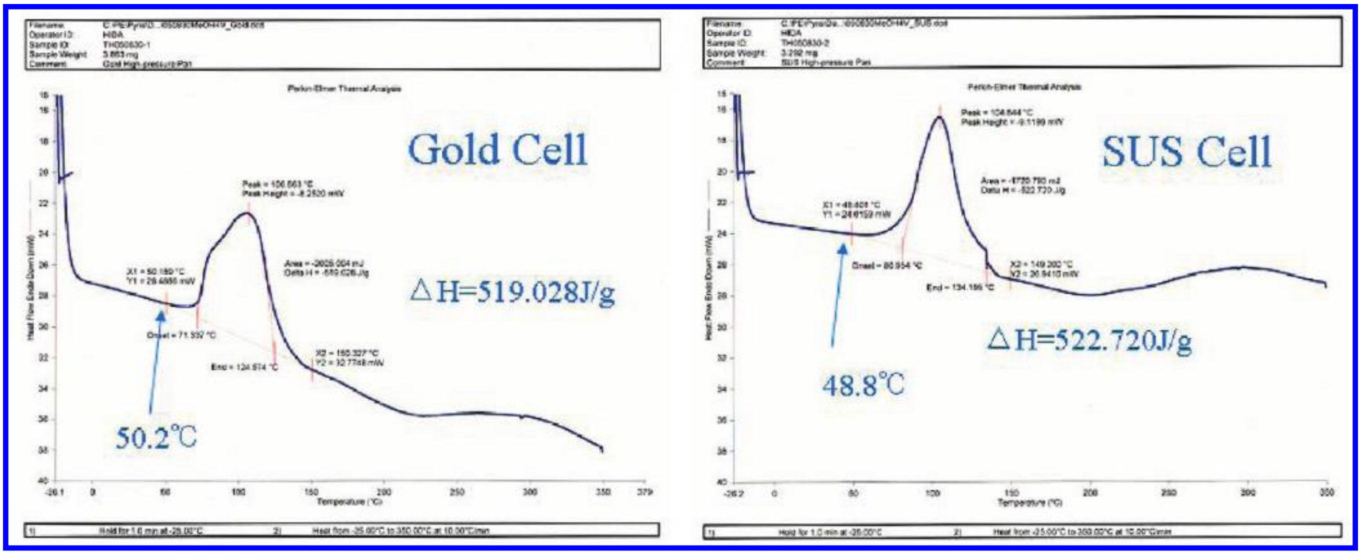


Figure 3. DSC chart of ozonized mixture (1.83 mol/L).

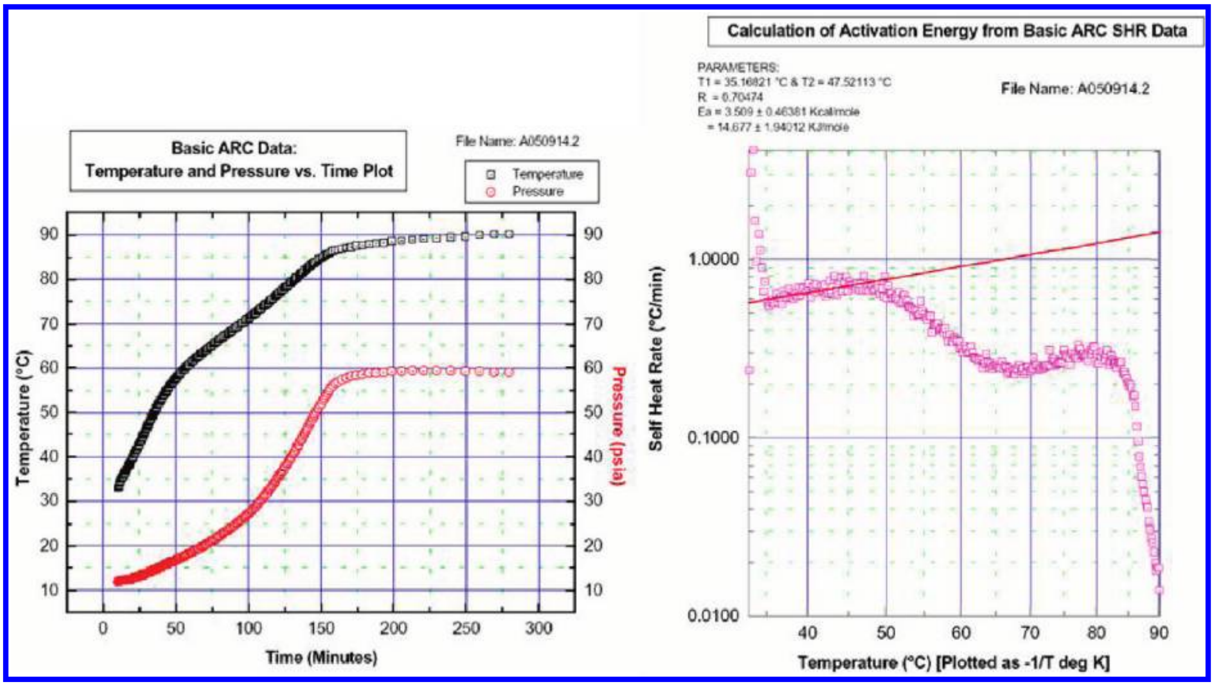


Figure 4. **ARC chart of ozonized mixture (1.83 mol/L).**

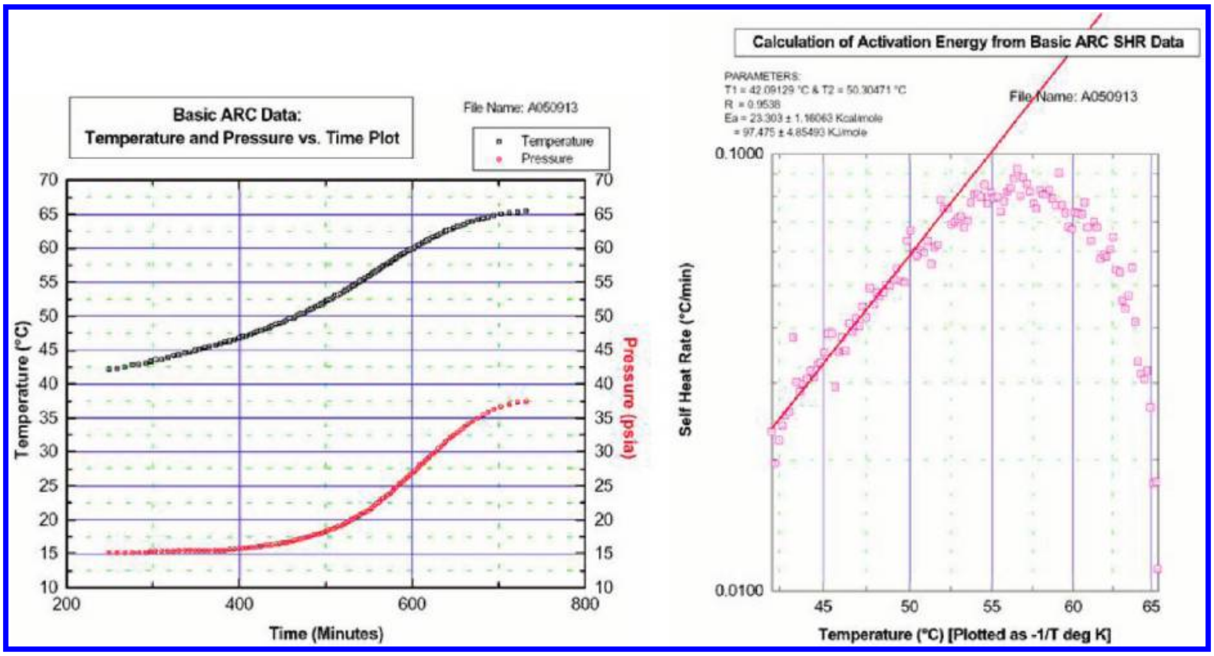


Figure 5. **ARC chart of ozonized mixture (0.73 mol/L).**

Table 3. **Result of RC1e experiment**[a]

process temperature (°C)	ΔH_{reac} (kJ/mol)	specific heat of reaction mass (J/(g·K))	$\Delta T_{\mathrm{ad}}{}^{b}$ (K)
−40	498.95	2.15	185.9

[a] Ozonolysis was carried out with 0.36 mol/L of **2**. [b] Corrected value of 0.73 mol/L.

assurance. The maximum temperature of the synthetic reaction (MTSR) was calculated at each temperature (Table 4). MTSR by dropwise addition of trimethyl phosphite at −25 to −10 °C for 90 min was below ADT_{24}, which means that the risk of a runaway reaction by self-heating decomposition is not very large. The time maximum rate (TMR) at −10 °C is 7.6 × 10^4 h; thus, there is no problem such as exceeding the upper limit temperature of reductive decomposition.

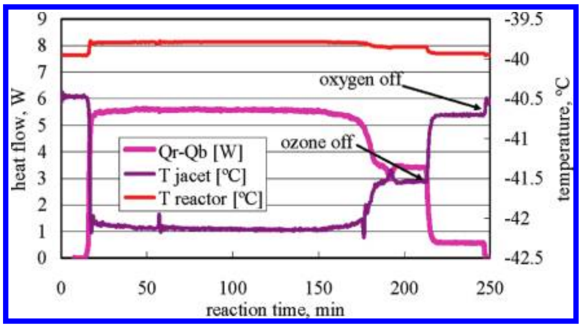


Figure 6. **Heat flow of ozonolysis of 2.**

Table 4. **RC1e experimental results of reduced decomposition of ozonized mixture and MTSR**[a]

process temperature (°C)	ΔH_{reac} (kJ/mol)	specific heat of reaction mass (J/(g·K))	heat accumulation (%)[b]	ΔT_{ad} (K)[c]	MTSR[d]
−25	429.25	2.52	33.3	140.24	25.36
−10	442.39	2.52	25.0	144.61	27.80

[a] Experiment was carried out using 0.37 mol/L of ozonized solution of **2**. [b] Heat accumulation at dropwise addition of 1.0 equiv. of trimethyl phosphite. [c] This value is converted to the solution of 0.73 mol/L of **2**. [d] MTSR $= T_P + (1 - X_{ST}/100) \times \Delta T_{ad} \times M_F/M_{ST}$ (T_P: Process temperature, X_{ST}: Conversion at dropwise addition of stoichiometric reagent, M_{ST}: Mass of reaction mixture at dropwise addition of stoichiometric reagent, M_F: Mass of reaction mixture at finish of dropwise addition, ΔT_{ad} adiabatic temperature rise of reaction heat.). Dropwise addition time of trimethyl phosphite.

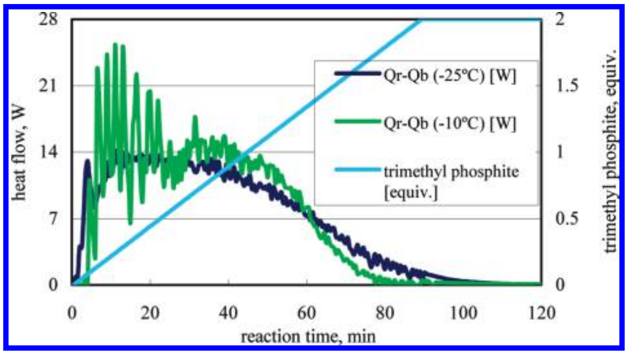


Figure 7. **Heat flow of reductive decomposition of ozonized mixture.**

Other Risk Assessments. Ozonolysis of **2** in methanol gave ozonide **9** as well as **10**. Reduction of **9** proceeded with difficulty, which compares with that of **10**. The remaining **9** can cause an explosion on distillation of **3**. Reductive decomposition of **9** was accelerated by addition of sulfuric acid at room temperature. The subsequent operation was carried out only after the complete termination of reductive decomposition of **9** was confirmed.

The **3** obtained was extracted with toluene and condensed under reduced pressure. The thermal stability of the residue was evaluated with ARC. Its ADT$_{24}$ is calculated as 113.5 °C and TMR at 100 °C is 1.32×10^3 h. A high-performance pump, which can reduce the pressure to at least below 20 mmHg, is necessary to distill **3** at below 100 °C of jacket temperature.

Conclusion

A risk assessment and safety evaluation studies for ozonolysis of *β*-pinene were conducted in detail. The thermal stability of the ozonized mixture was clarified by DSC and ARC measurement and the accumulation of heat of the reductive decomposition was investigated by RC1e. In conclusion, the hazardous points of ozonolysis are: the thermal instability of the products due to a high concentration of the reaction mixture, the process temperature of ozonolysis, the process temperature of reductive decomposition, dropwise addition time of the reducing reagent and complete decomposition of ozonide. Particularly hazardous is the accumulation of heat at the reductive decomposition, requiring careful operation and control of the process temperature. Twenty-seven batches of pilot manufacturing on a 17 kg/lot of **2** basis were achieved successfully according to the safety evaluation study.

Experimental Section

NMR spectra were measured on a Varian^{Unity} Inova-500 or Inova-600. DSC was measured on a Perkin-Elmer Pyris 1. ARC was measured by Asahi Kasei Chemicals Corporation Explosives R&D Center.

Procedure for Manufacturing of (+)-nopinone 3 in a Pilot Plant. In a SUS reactor (300 L), *β*-pinene **2** (17.0 kg, 124.8 mol) was mixed with methanol (150 kg, 187 L), and the mixture was cooled to −57 °C and stirred with a stream of ozonized oxygen gas for 8 h. The reaction was checked for completion by TLC, and then the mixture was heated to −27 °C. Trimethyl phosphite (31 kg, 249.8 mol) was added dropwise under the same conditions for over 3 h. The reaction mixture was heated to 0 °C for 1 h, and aqueous 10% H_2SO_4 (50 kg) was added. After stirring at 25 °C for 4 h, the disappearance of ozonide **9** was checked by TLC. After the checking for disappearance of peroxide using KI starch paper, the reaction mixture was transferred to glass-lined reactor (1000 L). Toluene (88 kg, 102 L) and water (340 kg) was added and stirred. The organic layer was separated and washed with aqueous 5% $NaHCO_3$ (85 kg), followed by aqueous 10% Na_2SO_3 (42.5 kg). The aqueous layer was extracted by toluene and then separated. The organic layers were combined. After the removal of toluene, the residue was distilled under 5 mmHg at 90−100 °C of jacket temperature and gave (+)-nopinone **3**[11] (11.25 kg, 65.2%, boiling point at 5 mmHg: 78−80 °C).

Acknowledgment

We thank Ms. Mao Kuriyama and Mr. Shuji Kawabe in Asahi Kasei Chemicals Corporation Explosives R&D Center for measurement of ARC and helpful discussions on safety evaluation study.

Supporting Information Available

Copies of two-dimensional NMR spectra of **3**, **9**, and **10**; copies of TLC for checking reaction termination; ARC chart of residue of (+)-nopinone **3**, and summarized table of ARC measurements. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Murray, R. W. *Acc. Chem. Res.* **1968**, *1*, 313.

(14) CHETAH has been developed by ASTM (American Society for Testing and Materials), which can calculate the released energy of organic compound under ideal gas state.

(15) ARC® use sample container of anti pressure type, and some of exothermal heat of decomposition can be consumed for heating of sample container. Therefore experimental value must be corrected by correction factor φ. $\varphi = 1 + [M_W \times C_{PW}/(M_S \times C_{PS})]$ (M_W: mass of container, C_{PW}: specific heat of container, M_S: mass of sample, C_{PS}: specific heat of sample).

(16) ADT$_{24}$ (adiabatic decomposition temperature for 24 h) is the temperature at which time to maximum rate (TMR) is 24 h.