Organic Process Research & Development **2007**, *11,* 762–765

Communications to the Editor

Execution of a Performic Acid Oxidation on Multikilogram Scale

David H. Brown Ripin,* Gerald A. Weisenburger,* David J. am Ende, David R. Bill, Pamela J. Clifford,
Clifford N. Meltz, and James E. Phillips

Chemical Research and Development, Pfizer Global Research Division, Pfizer Inc., Eastern Point Road, Groton, Connecticut 06340, U.S.A.

Abstract:

In order to run a peracid oxidation on multikilogram scale in a pilot plant facility with an acceptable level of risk, an extensive study of the thermal characteristics of the reaction, reactants, and quench was undertaken. A number of features were engineered into the process in order to confidently run the process without the potential for a thermal or pressure excursion on scale.

Introduction

CP-865,569 (**8**) is a CCR1 antagonist. The candidate contains a tertiary amine and the unusual benzylic sulfonic acid functionalities and exists as a zwitterion as its neutral species. The synthesis of this candidate involved a number of synthetic and processing challenges due to the interesting functionality present and the physical properties thereof. Herein is described execution of the peracid oxidation of thioacetate (**9**) to CP-865,569 on multikilogram scale.

Caution: The processes described herein have the potential to release large amounts of energy and gas in an uncontrolled fashion. Investigators considering running a large-scale oxidation reaction should consult the literature, run appropriate safety tests, and take proper precautions when running the reaction.

Why Use a Peracid Oxidation?

The original synthesis of the candidate installed the sulfonic acid functionality utilizing a sulfite displacement[1] (Scheme 1). While the installation of the sulfonic acid proceeded in reasonable selectivity relative to sulfite ester formation (S vs O alkylation ratio 9:1), the primary problem with this route was the extreme difficulty encountered when trying to remove sodium from the material prior to forming the desired salt. For this reason, a method which introduced the sulfonic acid at the end of the synthesis in the absence of metal counterions was sought.

Identification of a New Method for the Introduction of the Sulfonic Acid. The chloride could be very cleanly displaced by tritylmercaptan or potassium thioacetate (Scheme 2). Either product could then be oxidized under a variety of conditions, including some metal-ion-free conditions such as performic or peracetic acid in formic or acetic acid.[2] Under the acidic conditions, no *N*-oxide formation was observed. The crystallinity of the thioacetate derivative in conjunction with the higher atom efficiency and lower cost as compared with the trityl protecting group led us to focus our attention on the thioacetate route.

The success of the new route hinged upon the ability to cleanly oxidize thioacetate **9** and quench the reaction in the absence of any metal-ion-containing salts. This could be accomplished using a performic acid or peracetic acid oxidation followed by quenching of the excess peroxide with activated carbon (Darco G-60).[3] A number of issues were identified that needed to be addressed in order to confidently run this process on scale. First and foremost, the thermal stability of the peracid reagent and the heat output from the reaction itself required study. Further, the quench of the reaction generates heat and oxygen gas, a situation requiring control in a bulk manufacturing facility. Finally, in the case of the performic acid oxidation, the stability of formic acid during the subsequent distillation required investigation.

Thermal Potential of the Oxidants. Performic acid and peracetic acid are generated in situ by the addition of hydrogen peroxide to the corresponding carboxylic acid.[4] A solution of performic acid was made by adding 1.0 volume of 30 wt % hydrogen peroxide to 2.5 volumes of 96 wt % formic acid. The performic acid solution and a commercial solution of 32 wt % peracetic acid in acetic acid were tested by differential scanning calorimetry (DSC) which indicated that these solutions decompose at relatively low temperatures with the generation of a large amount of heat. DSC screening of **8**, **9**, and 96 wt % formic acid did not reveal any significant thermal concerns for this process.

Accelerating rate calorimetry (ARC) was conducted to accurately determine the onset temperature and to investigate off-gassing. Analysis of the performic acid solution by ARC,

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* Authors to whom correspondence should be addressed. G.A.W.: E-mail: gerald.a.weisenburger@pfizer.com; D.B.R.: E-mail: david.b.ripin@pfizer.com.

(1) For a full synthetic report, see: Belecki, K.; Berliner, M.; Bibart, R. T.: Meltz, C.; Ng, K.; Phillips, J.; Brown Ripin D. H. *Org. Process Res. Dev.* **2007**, *11*, 754−761.

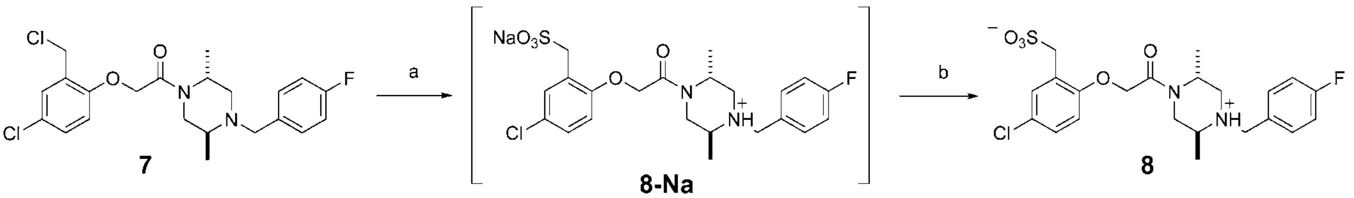
(2) Oxidation of thioacetates to sulfonic acids: Koenig, N. H.; Swern, D. *J. Am. Chem. Soc.* **1957**, *79*, 4235.

(3) Residual metals in the activated carbon are postulated to be the active catalyst in this reaction. No lot-to-lot variability was observed in the effectiveness of the quench, either between different lots of the same grade of carbon, or other types of carbon (KBB was also tried). Each lot was use-tested prior to use on scale.

(4) For a review of organic peracids see: Swern, D. *Chem. Rev.* **1949**, *45*, 1.

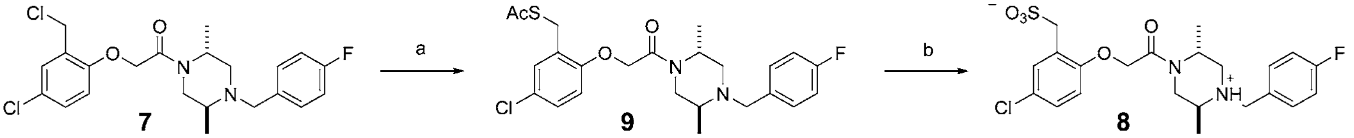
10.1021/op700039r CCC: $37.00

Scheme 1. **Original synthesis of CP-865,569 using a sulfite displacement**[a]



[a] Reagents and conditions: a) Na_2SO_3, MeCN, b) HCl, MeCN, *i*-PrOH.

Scheme 2. **Installation of the sulfonic acid functionality of CP-865,569 via oxidation of thioacetate 9**[a]



[a] Reagents and conditions: a) KSAc, PhMe, b) HCO_2H, 30% H_2O_2 in H_2O or 30% AcOOH in AcOH.

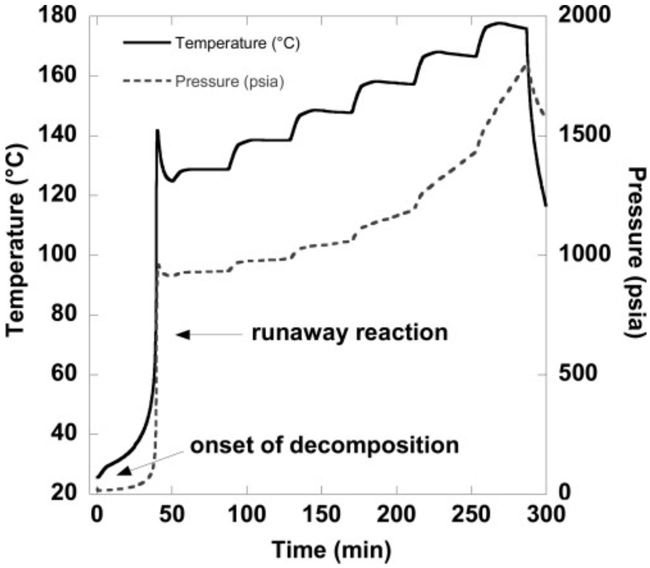


Figure 1. **Accelerating rate calorimetry (ARC) of 1.0 vol. 30 wt % H_2O_2 in 2.5 vol. formic acid (14.6 wt % performic acid assuming 100% conversion); 5 °C , ϕ-corrected onset temperature, 179 °C adiabatic temperature rise (ATR), 252 °C/min maximum temperature rate, 1972 psi/min maximum pressure rate.**

Figure 1, revealed a ϕ-corrected onset temperature of 5 °C.[5] The exotherm was severe and rapid, resulting in a ϕ-corrected adiabatic temperature rise (ATR) of 179 °C and a maximum self-heat rate of 252 °C/min. The time to maximum rate (TMR) was 30 min at 25 °C under these experimental conditions. The TMR is the time required to reach the maximum rate from the initial time of onset. As a general rule, a TMR of greater than 24 h at the processing temperature is considered to be acceptable in a manufacturing facility, providing sufficient time for corrective action if cooling, stirring, or other critical utilities are unexpectedly interrupted. In addition to the thermal event, a maximum pressure rise of 1972 psi/min was observed. The decomposition generated a non-condensable gas as indicated by a residual pressure of 861 psia upon cool down to 22.7 °C. It is clear from these results that accumulation of performic acid could lead to severe consequences.

Investigation of a commercial solution of 32 wt % peracetic acid in acetic acid by ARC revealed two exotherms. The first exotherm occurred at a ϕ-corrected onset temperature of 30 °C with an ATR of 358 °C, a maximum temperature rate of 2000 °C/min, and a 3.5 h TMR at 30 °C.[6] A maximum pressure rate of 1479 psi/min and a residual pressure of 400 psia upon cool down to 20.8 °C were observed. The experiment terminated during the second exotherm because the 300 °C limit was reached.

Oxidation with peracetic acid would have been the preferred method for a number of reasons: peracetic acid is more stable than performic acid,[7] the oxidation of **9** proceeds at a lower temperature and is therefore dose controlled at a lower temperature, and the isolation does not involve the distillation of formic acid, which poses a possible hazard if purified to a high grade during distillation. Unfortunately, peracetic acid does not form as readily as performic acid on addition of hydrogen peroxide to acetic acid.[8] As a result, in order to run a peracetic acid oxidation, a preformed solution of peracetic acid would have to be purchased and stored in bulk quantities. Alternatively, addition of acetic anhydride to an acetic acid solution of **9** followed by addition of hydrogen peroxide did give facile oxidation at 0 °C. However, peracetic acid generated under anhydrous conditions has been reported to explode.[9] Therefore, we chose to oxidize multikilogram quantities of **9** with performic acid generated in situ.

RC1 Experiments. RC1 calorimetry was performed to determine: (1) The heat of the overall oxidation process, which includes (a) the heat of reaction of formic acid with H_2O_2 to give performic acid and (b) the oxidation of **9** by performic acid to give **8**. (2) The rate at which the heat is

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(5) Experiment was carried out using a titanium bomb and a ϕ-factor of 1.69. A corrected onset of −1 °C was observed when the experiment was repeated in a glass bomb with a metal stem and a ϕ-factor of 3.62.

(6) Experiment was carried out using a titanium bomb and a ϕ-factor of 2.42. A corrected onset of 41 °C was observed when the experiment was repeated in a glass bomb with a metal stem and a ϕ-factor of 4.43. The MSDS from FMC reports: SADT > 55 °C for a 55-gal drum (35 wt % peracetic acid solution in acetic acid).

(7) This is not a direct comparison since we did not test a 32 wt % solution of performic acid.

(8) When the process was repeated using acetic acid instead of formic acid, no product was observed at the end of the H_2O_2 addition. These relative rates of peracid formation have been noted in the literature, see ref 4.

(9) Urben, P.G., Ed. *Brethericks Handbook of Reactive Chemical Hazards*, 6th ed.; Butterworth-Heinemann: Woburn, MA, 1999; p 1627.

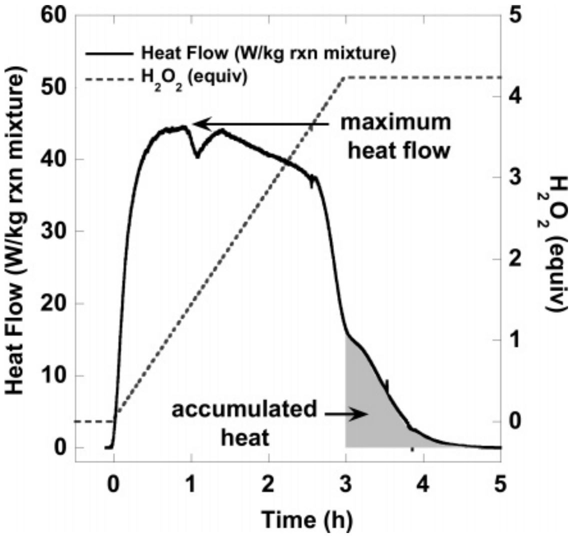

Figure 2. **RC1 data for a 3-h addition of 100 g of 30 wt % H_2O_2 to a solution of 99.7 g of 9 in 305 g (250 mL) of 96 wt % formic acid. $\Delta H_{rxn} = -975$ kJ/mol of 9, ATR = 172 °C, 9% thermal accumulation.**

released throughout the process. (3) The amount of thermal accumulation.

The oxidation was carried out by charging 4.2 equiv of 30 wt % H_2O_2 over 3 h to a solution of **9** in 2.5 volumes of formic acid maintained at 25 °C. The heat flow data is shown in Figure 2. The heat generated by the overall process, −975 kJ/mol of **9**, was determined by integrating the area under the heat-flow curve.[10] The ATR was calculated to be 172 °C using the integrated heat, final reaction mass, and final heat capacity, 2.33 J/g °C, of the reaction mass. The maximum heat flow, −44 W/kg of final reaction mixture, would challenge the cooling capacity of the scale-up equipment since we planned to maintain the batch temperature throughout the addition. Since the reaction heat was nearly dose controlled, with 9% thermal accumulation for the 3 h addition, the maximum heat flow could be easily reduced by slowing the addition rate.[11]

The reaction quench was also investigated using the RC1. The crude reaction mixture was charged over 1 h to a slurry of G-60 Darco maintained at 25 °C. The heat for this process was determined to be −135 kJ/mol of **9**, resulting in a 17 °C ATR. The maximum heat flow was −37 W/kg of reaction mixture with 40% thermal accumulation for the 1 h addition. Off-gassing was observed at a maximum rate of 40 L h^{-1} kg^{-1} of H_2O_2. This gas could easily be vented without pressurization of the scale-up equipment. With this data in hand, engineering controls for the scale-up were proposed and implemented.

Pilot-Plant Preparation

Safety Considerations and Engineering Controls. *Tank Preparation.* Trace metal impurties can catalyze the decomposition of H_2O_2 into O_2 and H_2O and potentially lead to a foaming or over-pressurization incident. Therefore, spark testing of the vessel, agitator, baffle, etc. was performed to ensure the integrity of the glass lining. In addition, careful consideration was given to all parts that were to contact the reaction mixture to ensure compatibility with peroxide species. Passivation of the equipment with 35 wt % HNO_3 was considered but deemed unnecessary after discussions with the H_2O_2 manufacturer. Careful cleaning of the reaction vessel was also performed to reduce the risk of rapid decomposition caused by contaminants.

H_2O_2 Charge. Given the low onset temperature and high decomposition energy of performic acid, engineering controls were implemented to prevent accumulation. Vent-sizing studies showed that a rapid addition of the 30 wt % H_2O_2 would result in a runaway reaction producing a large amount of heat and pressure, highlighting the importance of a controlled addition. In order to eliminate the potential for a rapid addition, the 30 wt % H_2O_2 charge was subdivided into nine portions. Given the 172 °C ATR, subdivision of the H_2O_2 charge into nine portions should provide an acceptable safety margin, since in the worst-case, a 44 °C reaction temperature would result from rapid addition of one subdivision. In order to confirm the validity of this assumption, the vent-sizing experiment was repeated using one-ninth of the H_2O_2 charge, resulting in small increases in both temperature and pressure.

During the scale-up runs, the reaction was monitored by in situ IR and grab sample HPLC assay to confirm progression of the reaction and consumption of the peroxide. ARC analysis of the crude reaction mixture prior to quench revealed a maximum self-heating rate of about 0.1 °C/min, a minimal thermal hazard. Stirring and cooling was continued after reaction completion to remove any heat resulting from decomposition of the crude reaction mixture.

Quench. The oxygen off-gassing posed both a foaming and explosion potential.[12] A rapid nitrogen purge was maintained throughout the quench in order to prevent the oxygen level from rising above the LOC of formic acid. G-60 Darco was used at 5 wt % relative to **9**. An increase in the amount of carbon used in the quench led to more vigorous gas generation and a significant decrease in isolated yield of product. Quench completion was monitored with semi-quantitative peroxide test strips, which indicated a final peroxide concentration of less than 1 ppm. Prior to proceeding in our pilot plant, an ARC test was run on the quenched solution to confirm no exotherms would be observed during concentration. We considered using small tubing to transfer the crude reaction mixture to the Darco slurry to prevent rapid addition, but felt that it was not necessary due to careful operator training, the relatively low heat flow, and the relatively low rate of oxygen generation.

Isolation of the Product. Azeotropic drying with acetic acid under reduced pressure, followed by addition of methanol and precipitation with isopropyl ether provided

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(10) Integration was performed on a curve plotted as W versus seconds.

(11) Note that the percent accumulation was calculated based on the heat evolved after 4.2 equiv of H_2O_2 were added. Theoretically, only 3 equiv of H_2O_2 are needed for conversion of the thioacetate to the sulfonic acid. An accumulation of 34% was calculated after 3 equiv of H_2O_2 were added in the RC1 experiment.

(12) The limiting oxygen concentration of 96 wt % formic acid was determined to be 7.26−7.72% by Chilworth Technology.

solid zwitterion isolated by filtration. High purity formic acid is known to liberate carbon monoxide upon heating.[13] Therefore, acetic acid was added to the quenched reaction mixture prior to distillation. DSC and ARC analysis of the pot residue from a laboratory pilot at the start, midpoint, and end of the distillation did not reveal any significant exotherms or pressure events.

Summary of Pilot Plant Runs and Results. In execution, five runs of this process were performed in our pilot plant on 30−35-kg scale without incident, and produced product in high purity and >90% yield.[14] The oxidation reaction was run in a 300-gal tank with a maximum operating volume of 100 gal to provide a large headspace as an extra layer of protection. Likewise, the quench was executed in a 500-gal tank to provide a large headspace.

Experimental Section

DSC experiments were performed using a Mettler Toledo 822e instrument with a 20-min isothermal hold at 30 °C followed by a 4 °C/min scan rate to 300 °C in 40-μL, high-pressure (150 bar max), sealed, gold plated steel pans under an air atmosphere. ARC experiments were performed under an atmosphere of air using a clamshell style ARC from TIAX (Acorn Park, Cambridge, MA) with either a titanium or glass bomb with a 1/8 in. neck. Heat−wait−search experiments were perfomed starting at 30 °C in 10 °C steps with a sensitivity of 0.02 °C/min. Reaction heats were measured using a Mettler Toledo Mid-Temp RC1e with a 1-L MP06 reactor, Hastelloy C head, Hastelloy C anchor stirrer under a small positive pressure of nitrogen. The reactor was passivated with 35 wt % HNO_3 at 50 °C for 1 h followed by 3 × 1 L water rinses. The reactor was rinsed with acetone and blown dry with nitrogen overnight. Linear doses were performed using an integrated prominent pump and balance. The reaction temperature was maintained at 25 °C by allowing the jacket temperature to fluctuate. QuickCal calibrations were performed before additions and after reaction completion to obtain heat capacities and heat transfer coefficients. The heat flow curve was analyzed using WinRC NT version 7.11 (SR-6) with the following equation:

$$Q = Q_{\text{accum}} + Q_{\text{flow}} + Q_{\text{dose}}$$

Heat transfer coefficients were interpolated proportional to virtual volume, heat capacities were interpolated proportional to the reaction mass, and the baseline was interpolated proportional to conversion.

(2-(2-((2*R*,5*S*)-4-(4-Fluorobenzyl)-2,5-dimethylpiperazin-1-yl)-2-oxoethoxy)-5-chlorophenyl)methanesulfonic Acid (8). To a nitrogen-purged reactor at 20 °C is added solid 1-((2*R*,5*S*)-(4-(4-fluorobenzyl)-2,5-dimethylpiperazin-1-yl)-2-(4-chloro-2-(acetoxythiomethyl)phenoxy)ethanone (**9**) (34.2 kg,71.3 mol) and 96% formic acid (7.20 L/kg ethanethioate). To the formic acid solution at 20 °C is added one subdivision of 30 wt % hydrogen peroxide (3.40 kg, 3.77 L, 0.42 equiv). The exotherm is noted, and the temperature rise is recorded. The reaction is stirred at 20 °C for 2 h followed by the addition of a second aliquot of 30 wt % hydrogen peroxide (3.40 kg, 3.77 L, 0.42 equiv). Again, the exotherm is noted, and the temperature rise is recorded. The reaction is stirred at 20 °C for 2 h. The reaction mixture is sampled and analyzed by HPLC to monitor starting material consumption and sulfonic acid formation. (A lack of starting material consumption and sulfonic acid formation implies a buildup of hydrogen peroxide, and subsequent additions should be discontinued.) Upon determination of safe hydrogen peroxide consumption, the reaction mixture is treated with seven further subdivisions of 30 wt % hydrogen peroxide (each subdivision: 3.40 kg, 3.77 L, 0.42 equiv) with 2-h reaction times at 20 °C in between each subdivision. Samples for HPLC analysis are taken following subdivision 5 and 8 to confirm peroxide consumption. Upon complete addition of hydrogen peroxide, the reaction mixture is added to a suspension of 96% formic acid (39 L) and Darco G-60 (1.70 kg) at 20 °C under a high-volume nitrogen sweep over 2 h. A gentle gas evolution is noted and confirms a controlled consumption of excess hydrogen peroxide. The resulting suspension is stirred at 20 °C for 12 h, and a reaction sample is analyzed by accelerating rate calorimetry (ARC) to ensure complete peroxide consumption. The quenched reaction is filtered through Celite, and the filtrate is diluted with glacial acetic acid (316 L). The resulting solution is concentrated under reduced pressure to a volume of approximately 30 L with a maximum pot temperature of 50 °C. The desired **8** is diluted with methanol (140 L) and added to isopropyl ether (1400 L) at 20 °C over 1 h. The resulting slurry is stirred at 20 °C for 2 h followed by filtration, washed with isopropyl ether (35 L), and vacuum dried at 50 °C to afford **8** in 91% yield.

Acknowledgment

We thank Professor Steven Ley and Drs. Robert Dugger, Tamim Braish, Stephane Caron, and John Ragan for helpful discussions. We also thank Kyle Leeman and Natalie Harner for analytical assistance. Jeff Adler, Paul Allard, Joseph Bellavance, Todd Carden, Wayne Crandall, Douglas Davis, Thomas Limani, Larry Lumbert, Brian Morgan, Alden Peckham, Steven Stott, Ralph Scheck, III, Scott Schelkly, and Walden Smolen are thanked for operating the chemistry in pilot-plant equipment.

Received for review February 14, 2007.

OP700039R

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(13) (a) For details on formic acid, see: http://www.basf.com. (b) Reference 9, p 163.

(14) The process as performed on scale used 7.2 volumes of 96 wt % formic acid instead of 2.5 volumes as in the RC1 run.