

Safety and Environmental Reports

Oxidation of 4-Halo-2-nitrotoluene with Tetrabutylammonium Permanganate in Pyridine: Development and Safety Evaluation

Xiaohu Deng,^{*,†} Stephen Stefanick,[‡] Marna C. W. Pippel,[†] and Neelakandha S. Mani[†]

Department of Drug Discovery, Johnson & Johnson Pharmaceutical Research & Development, LLC, 3210 Merryfield Row, San Diego, California 92121, U.S.A., and Johnson & Johnson Pharmaceutical Research & Development, LLC, Research B-158, 1000 Route 202, Raritan, New Jersey 08869, U.S.A.

Abstract:

4-Halo-2-nitrobenzoic acids are synthesized by oxidation of 4-halo-2-nitrotoluene with tetrabutylammonium permanganate (TBAP) in pyridine in multigram quantities. A significant induction period is observed at room temperature, and the vigorous exothermic reaction presents the risk of a run-away reaction. By control-feeding cold TBAP into the reaction mixture at 60 °C, the initiation process is managed, and the reaction is safely performed on multigram scale. However, larger-scale reaction is NOT recommended, and use of appropriate equipments is strongly encouraged.

Introduction

The use of permanganates as general, versatile, oxidation reagents in research laboratories as well as in industry has an extensive history, which goes back to the nineteenth century.¹ Oxidation of substituted toluenes with inexpensive, readily available KMnO₄ in water is a classic reaction for the preparation of substituted benzoic acids. However, due to the low solubility of organic substrates in water, this oxidation reaction often requires extended heating and a large excess of KMnO₄ while providing products in low yields. To solve this problem, a variety of organic permanganates have been synthesized and successfully applied to different oxidation reactions.² Unfortunately, the oxidation of substituted toluenes with organic permanganates to prepare substituted benzoic acids was rarely documented.³ Furthermore, no detailed studies on large-scale syntheses or safety evaluations, which would provide crucial information for process development, have been described.

Herein we report a practical synthesis of 4-halo-2-nitrobenzoic acids in excellent yields by oxidation of 4-halo-

Table 1. Oxidation of 4-halo-2-nitrotoluene

entry	reagents and conditions	results
1	KMnO ₄ , H ₂ O, reflux ⁴	35%
2	KMnO ₄ , MgSO ₄ , H ₂ O, reflux ⁵	40%
3	KMnO ₄ , CH ₂ Cl ₂ /H ₂ O, BnEt ₃ N ⁺ Cl ⁻ , rt ⁶	trace
4	KMnO ₄ , CH ₂ Cl ₂ /AcOH/H ₂ O, Adogen 64, reflux ⁷	trace
5	KMnO ₄ , acetone/H ₂ O, NaHCO ₃ , MgSO ₄ , rt ⁸	no reaction
6	KMnO ₄ , tBuOH/H ₂ O/AcOH, 50 °C	incomplete
7	KMnO ₄ , pyridine/H ₂ O, Bu ₄ N ⁺ Cl ⁻ , rt ⁹	incomplete
8	Bu ₄ N ⁺ MnO ₄ ⁻ , DCE, rt ¹⁰	no reaction
9	Bu ₄ N ⁺ MnO ₄ ⁻ , pyridine, rt	100%
10	NaOCl, RuCl ₃ /Bu ₄ N ⁺ Br ⁻ , DCE/H ₂ O, rt ¹¹	40% (50% SM)
11	Na ₂ Cr ₂ O ₇ , AcOH/H ₂ SO ₄ , reflux ¹²	incomplete
12	NaIO ₄ , RuCl ₃ , CCl ₄ /CH ₃ CN/H ₂ O, reflux ¹³	no reaction
13	Co(OAc) ₂ , N-hydroxyphthalimide, air, rt ¹⁴	no reaction

2-nitrotoluenes with tetrabutylammonium permanganate (TBAP) in pyridine. At room temperature, a significant, unpredictable induction period was observed, and a pronounced exotherm caused a serious safety concern. After carrying out careful safety evaluations, we found that, with proper precautions, this reaction could be run smoothly with up to 40 g by control-feeding TBAP into the reaction at 60 °C.

Results and Discussion

In connection with one of our drug discovery projects, 4-halo-2-nitrobenzoic acids were required in multigram quantities. Considering the availability of potential starting materials, we focused on the oxidation of the corresponding 4-halo-2-nitrotoluenes. A typical KMnO₄ oxidation in water afforded a 35% yield after 4 days at refluxing temperature with 6 equiv of KMnO₄ added in batches (Table 1^{4–14}, entry 1). Various common modifications of the KMnO₄ oxidation, such as the addition of cosolvents or the employment of phase-transfer reagents, were largely unsuccessful (Table 1,

* To whom correspondence should be addressed. E-mail: xdeng@prdus.jnj.com.

† San Diego, California.

‡ Raritan, New Jersey.

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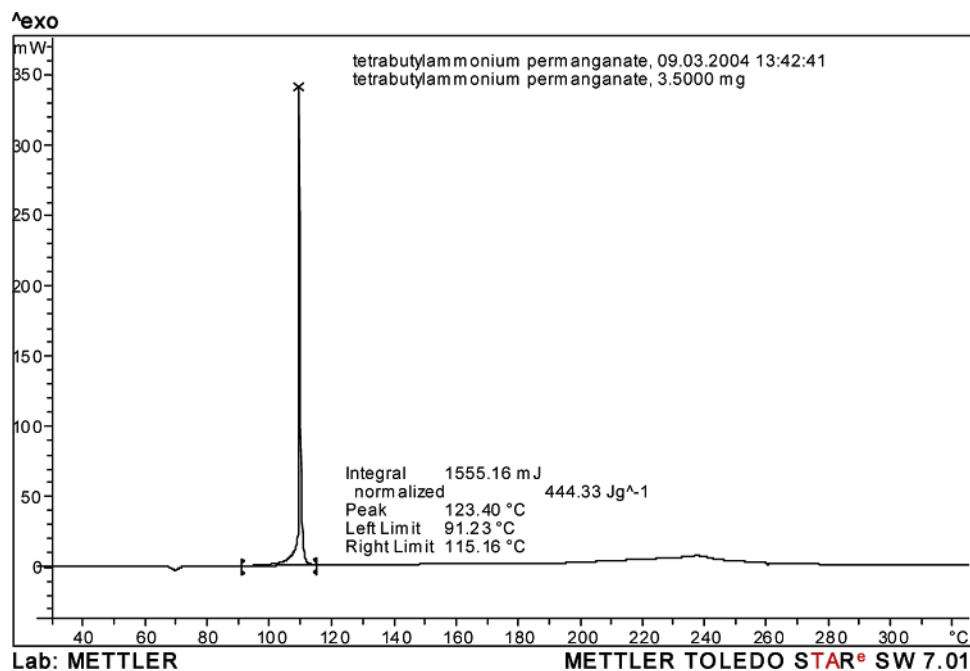
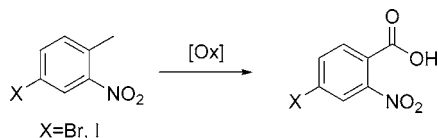


Figure 1. DSC test on TBAP.

entries 2–7). A number of other oxidation methods also gave unsatisfactory results (Table 1, entries 10–13). It is noteworthy that the $\text{RuCl}_3/\text{NaOCl}$ system was very mild and easy to handle (Table 1, entry 10). However, the reaction stalled at about 40% conversion.



We attributed the low yields of KMnO_4 oxidation reactions to the low solubility of the toluene substrates in water. We reasoned that an organic-soluble permanganate might have a better chance to succeed. Tetrabutylammonium permanganate (TBAP) was chosen because of its reported relative stability.¹⁵ Dichloroethane as the solvent resulted in no reaction (Table 1, entry 8). Interestingly, switching to pyridine as the solvent afforded quantitative conversion after several hours at room temperature (Table 1, entry 9). However, when we attempted to do the reaction on a larger scale (40 g), we identified a safety issue. When all the reactants were mixed at room temperature, an induction period that ranged from several hours to days was observed.

The length of the induction period seemed to be related to the water content in the system; the more water, the longer the induction period. Addition of various dehydration reagents such as MgSO_4 and molecular sieves did not help to eliminate the induction period. In addition, the oxidation reaction, extremely fast once initiated, was vigorously exothermic, which raised concern for a runaway reaction. In fact, the oxidation reaction of 4-iodo-2-nitrotoluene with TBAP in pyridine was peculiarly violent such that a runaway reaction was observed at 10-g scale.

The cause of the induction period remains unclear. We ruled out the possibility of a self-catalyzed reaction by performing the following experiment: TBAP (0.4 equiv) was added to the substrate solution in pyridine. After the TBAP was consumed and the benzoic acid product was formed, the rest of TBAP was added. Induction periods were observed on both additions of TBAP.

It is well-known that increasing temperature helps eliminate induction periods. However, because of the notorious instability of organic permanganates at elevated temperature,¹⁶ we decided to perform safety evaluations first. The thermal stabilities of the starting materials and the product were first tested on DSC. Whereas 4-halo-2-nitrotoluenes and 4-halo-2-nitrobenzoic acids were stable up to 200 °C, TBAP underwent a substantial exothermic decomposition that initiated at ~ 91 °C (Figure 1).

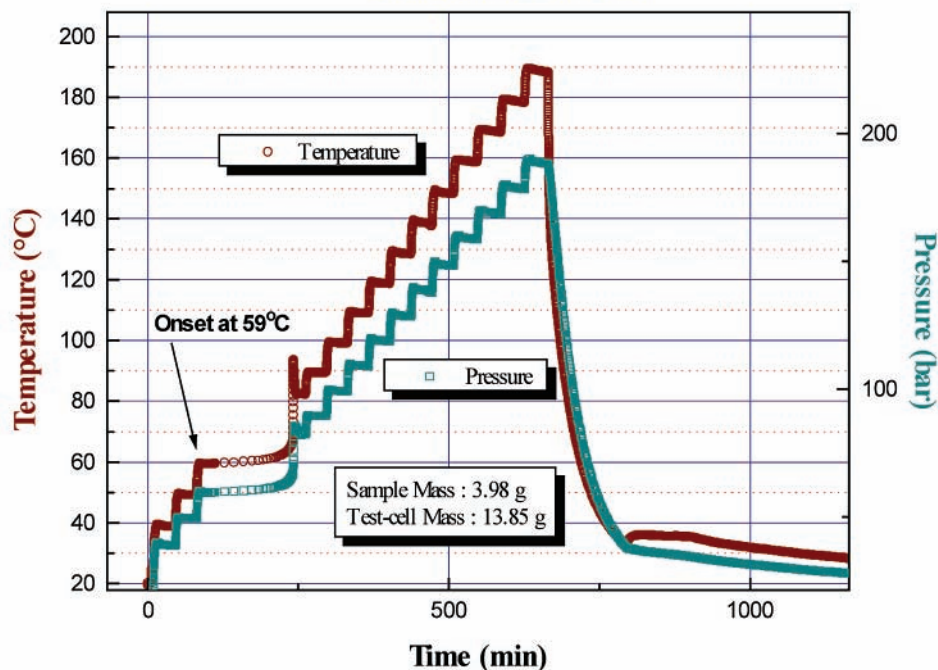
An ARC (accelerating rate calorimetry) test was then run on a solid TBAP sample. An exothermic decomposition was observed that initiated at 59 °C (lower than that observed in the DSC test), and the self-heating rate (SHR) exceeded 100 °C/min at its maximum, indicative of a highly unstable compound (Figure 2). The ARC test was also performed on a pyridine solution of TBAP (same concentration as that used in the reaction procedure). The solution was also thermally

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Temperature and Pressure as a Function of Time

EuroARC file : TBAPSALT

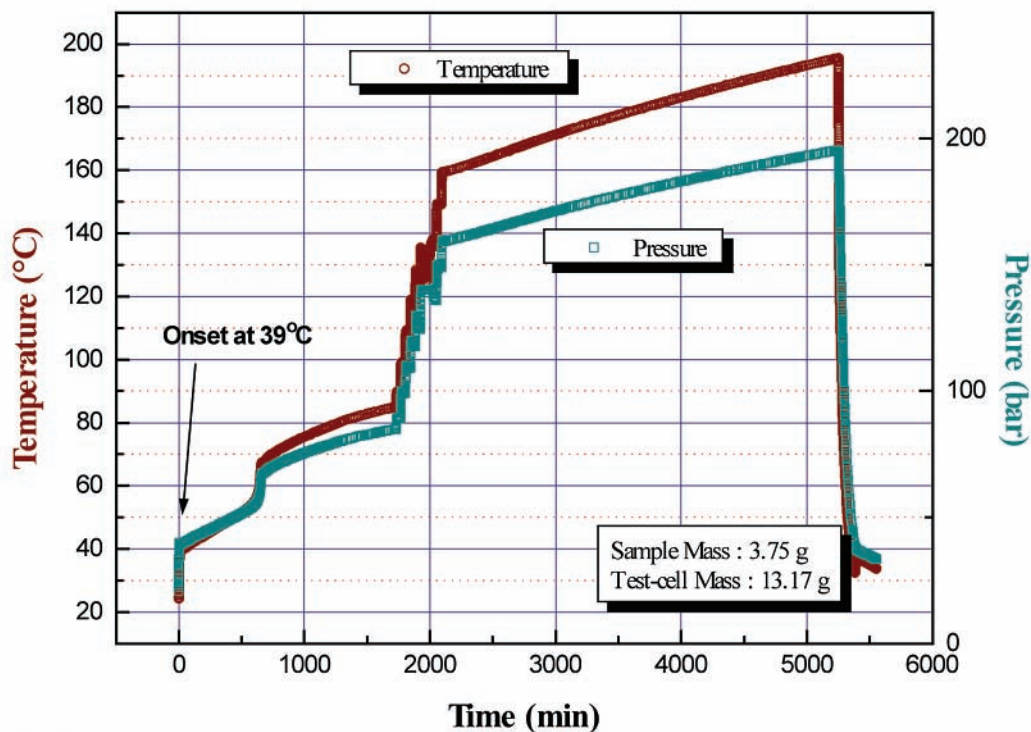


ARCCal: IuLi

Figure 2. ARC test on TBAP.

Temperature and Pressure as a Function of Time

EuroARC file : TBAPSOLN



ARCCal: IuLi

Figure 3. ARC test on a TBAP solution in pyridine.

unstable, and the exothermic decomposition started as low as 39 °C, although the rate of decomposition was slower than that observed for the neat solid (Figure 3).

In light of the DSC and ARC results, we decided to run this reaction by adding a cold pyridine solution of TBAP slowly to a 60 °C solution of the 4-bromo-2-nitrotoluene,

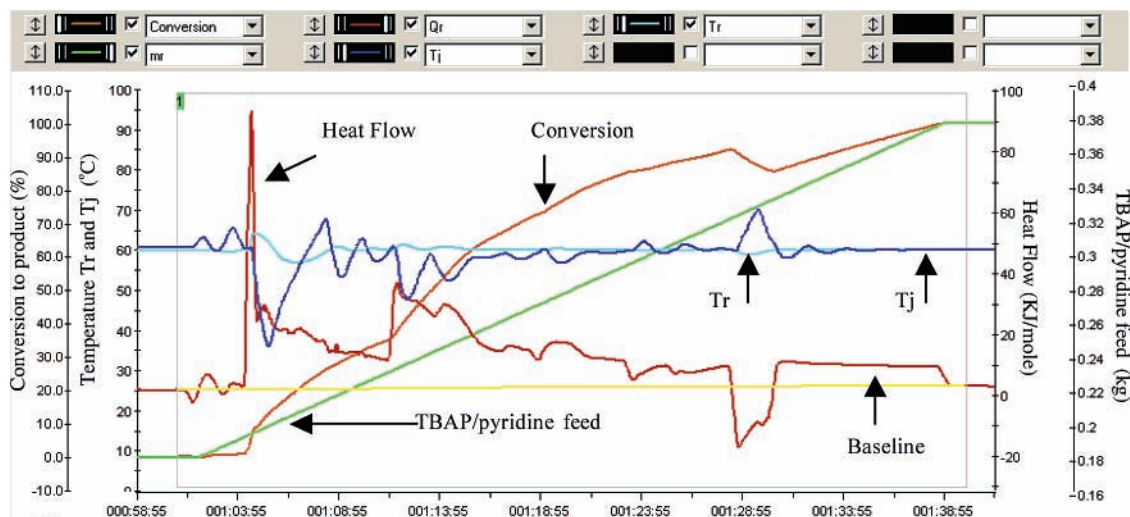


Figure 4. The RC-1 graph on the oxidation reaction. Orange = thermal conversion to product. Red = heat flow (ΔH_{rxn}). Green = TBAP/pyridine feed. Dark blue = jacket temperature, T_j . Light blue = reaction temperature T_r . $\Delta H_{\text{rxn}} = -23.94$ kJ/mol. Worst case temperature rise = 72 °C.¹⁸

with the hope that higher temperature would eliminate the induction period. The reaction was run in a 1.0-L SV01 vessel equipped with a Mettler Toledo RC-1 reaction calorimeter (Figure 4). The RC-1 graph showed that the reaction was an exothermic, feed-controlled addition (the green feed line and the orange conversion line were parallel). A noticeable, yet manageable, induction period was still observed at 60 °C during the initial stage of the reaction, demonstrated by the lack of deflection in the orange conversion line relative to the green feed line. Once the reaction began, an initial large exotherm was observed (evident by the sharp spike of the red line) that quickly subsided as the reaction progressed.¹⁷ During the initial exotherm period, the RC-1 jacket T_j had to be cooled to 36 °C to maintain the desired 60 °C reaction temperature. After that, the reaction equilibrated and then proceeded smoothly with the feeding of TBAP/pyridine. The reaction was completed in about 2.5 h, and an approximately 80% isolated yield was obtained.

In conclusion, oxidation of 4-halo-2-nitrotoluene with TBAP in pyridine is an efficient method to synthesize 4-halo-2-nitrobenzoic acid. However, the unpredictable induction period and the vigorously exothermic nature of the reaction pose a serious safety concern. We have developed a safer procedure to perform the oxidation at 60 °C by adding cold TBAP into the substrate solution in pyridine on multigram scale. Nonetheless, because of the thermal instability of TBAP and the difficulty of completely eliminating the induction period, this oxidation is not recommended for use on larger scale.

Experimental Section

All the reagents were purchased from commercial sources and used without further purification. Tetra-*n*-butylammonium permanganate was prepared according to a literature procedure¹⁵ and dried in a vacuum at room temperature. This

(17) The waviness of the red heat flow line is indicative of the variation associated with the use of a manual addition using a liquid dropping funnel for the TBAP/pyridine addition.

material decomposes slowly at room temperature over several months. Immediate use after preparation is recommended.

The DSC tests were performed on a Mettler Toledo model 822e DSC with 5.1 mg TBAP. Conditions were the following: 10 °C/min to 300 °C, sealed aluminum pan, nitrogen purge 80 mL/min. The ARC tests were performed on a CSI accelerating rate calorimeter with 3.1 g solid TBAP and a TBAP solution in pyridine. The conditions were standard ARC titanium test sphere with a 0.25 in. neck, air atmosphere, and standard heat/wait/search mode from 40 to 250 °C.

Initial Oxidation Procedure with Induction Periods.
4-Bromo-2-nitrobenzoic Acid. In a 2-L round-bottom flask equipped with a water bath, a reflux condenser, and magnetic stirring, 4-bromo-2-nitrotoluene (34.1 g, 158 mmol, 1.0 equiv) was dissolved in 300 mL of pyridine, and $\text{Bu}_4\text{N}^+\text{MnO}_4^-$ (120 g, 332 mmol, 2.1 equiv) was added at room temperature. Depending on different batches of the TBAP, the reaction could take a few hours to days to initiate. Once the reaction started, it proceeded vigorously and completed in a few minutes. *Caution: reaction temperature rose significantly almost to the boiling point of pyridine!*

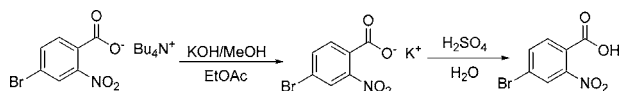
Workup and Isolation Procedures. Pyridine was removed by evaporation as much as possible, and then 300 mL of EtOAc and 200 mL of H_2O were added. The slurry was stirred at room temperature for 30 min. The precipitated brown solid (MnO_2)¹⁹ was filtered off and washed with EtOAc. The clear organic layer was washed with 5% H_2SO_4 aqueous solution (200 mL) twice and brine (200 mL) once, dried over MgSO_4 , and evaporated to afford a thick, light-brown oil. The crude product was dissolved in EtOAc (200 mL), and then KOH (8.9 g, 159 mmol, 1.0 equiv) in a minimal amount of MeOH (~ 30 mL) was added dropwise. After stirring at room temperature for 1 h, the precipitated

(18) The RC-1-calculated worst-case temperature rise was based on the scenario that the solution of the TBAP was accidentally added all at once. Coupled with the 60 °C starting temperature, the maximum temperature theoretically could reach 132 °C if accidental mischarge occurred. Therefore, a chemical reaction hazard exists for this reaction.

(19) Adding some NaHSO_3 sometimes helped the precipitation of MnO_2 .

solid was collected by filtration and washed with EtOAc. The filtrated solution was concentrated, and the precipitation was repeated with KOH in MeOH. The two crops were combined and dissolved in H₂O (~250 mL). Under vigorously stirring, concentrated H₂SO₄ was added carefully until pH < 2. The slurry was stirred at room temperature for 30 min. After filtration and washing with water, the white solid was dried under vacuum to give the desired product in >98% purity based on HPLC analysis (32.5 g, 132 mml, 83%).²⁰ Mp: 161–163 °C; lit. 164–165 °C.²¹

(20) Simply pouring the reaction solution into a cold aqueous NaHSO₃ solution resulted in the product oiling out as the tetrabutylammonium salt. By performing the above procedure, the potassium salt of the benzoic acid was precipitated out from EtOAc, thus efficiently removing the tetrabutylammonium cation. Acidification with H₂SO₄ solution precipitated out the pure 4-bromo-2-nitrobenzoic acid as a white solid in excellent purity.



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4-Iodo-2-nitro-benzoic acid. When the same procedure as above was used for the oxidation of 4-iodo-2-nitrotoluene, an induction period was also observed. This reaction was more vigorous, and a runaway reaction took place on a 10-g scale reaction.

Safer Oxidation Procedure. The experiment was performed in an SV01 1.0-L vessel equipped with a Mettler Toledo RC-1e reaction calorimeter and a propeller stirrer. 4-Bromo-nitrotoluene (9.1 g, 42 mmol, 1.0 equiv.) was dissolved in 200 mL of pyridine and heated to 60 °C. After the necessary calorimetric measurements, a 25 °C solution of TBAP (32 g, 89 mmol, 2.1 equiv) in pyridine (200 mL) was added slowly via a liquid dropping funnel to the 60 °C reaction mixture over approximately 35 min. The reaction was then stirred at 60 °C for 2 h and then cooled to 25 °C. After the workup and purification procedures as described above, 4-bromo-2-nitrobenzoic acid was obtained in 81% yield.

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