

Available online at www.sciencedirect.com



Tetrahedron

Tetrahedron 61 (2005) 10995-10999

Aerobic oxidation of 1,3,5-triisopropylbenzene using *N*-hydroxyphthalimide (NHPI) as key catalyst

Yasuhiro Aoki, Naruhisa Hirai, Satoshi Sakaguchi and Yasutaka Ishii*

Department of Applied Chemistry and High Technology Research Center, Faculty of Engineering, Kansai University, Suita, Osaka 564-8680, Japan

Received 20 July 2005; revised 20 August 2005; accepted 22 August 2005

Available online 16 September 2005

Abstract—The first systematic study on the aerobic oxidation of 1,3,5-triisopropylbenzene was examined by the use of *N*-hydroxyphthalimide (NHPI) as a key catalyst. It was found that 1,3,5-triisopropylbenzene was efficiently oxidized with O_2 in the presence of a catalytic amount of NHPI and azobisisobutyronitrile (AIBN) at 75 °C. Upon treatment of the resulting products with sulfuric acid followed by acetic anhydride led to 5-acetoxy-1,3-diisopropylbenzene and 3,5-diacetoxy-1-isopropylbenzene as major products and a small amount of 1,3,5-triacetoxybenzene. When *t*-butylperoxypivalate (BPP) was employed as a radical initiator, the oxidation could be achieved in good yield even at 50 °C. This oxidation provides a facile method for preparing phenol derivatives bearing an isopropyl moiety, which can be used as pharmaceutical starting materials.

© 2005 Elsevier Ltd. All rights reserved.

1. Introduction

Aerobic oxidation of alkylbenzenes is a very important industrial process for the production of primary chemicals and monomer materials. For instance, the aerobic oxidation of *p*-xylene to terephthalic acid is practiced in large scale in the chemical industry worldwide.¹ Another important aerobic oxidation is the conversion of isopropylbenzene to cumene hydroperoxide which on subsequent treatment with sulfuric acid affords phenol and acetone.² The aerobic oxidation of *m*- and *p*-diisopropylbenzenes leading to resorcinol and hydroquinone is also an important autoxidation process.³ In recent years, we have developed a new catalytic method for the aerobic oxidation of alkylbenzenes using *N*-hydroxyphthalimide (NHPI) as a key catalyst,⁴ and applied to the aerobic oxidation of *m*- and *p*-diisopropylbenzenes to develop an alternative route to resorcinol and hydroquinone.5

However, there has been little study so far of the aerobic oxidation of 1,3,5-triisopropylbenzene (1) except for several patent works.⁶ Therefore, the aerobic oxidation of 1 to obtain the corresponding phenol derivatives is thought to be interesting. In this paper, we would like to report the first systematic study on the aerobic oxidation of 1 using NHPI

as a key catalyst in the presence or absence of a radical initiator (Eq. 1).



2. Results and discussion

The oxidation of **1** under atmospheric dioxygen in the presence of NHPI and AIBN under various conditions is shown in Table 1.

Compound 1 (3 mmol) was reacted with atmospheric dioxygen (1 atm) under the influence of NHPI (0.3 mmol) and AIBN (0.09 mmol) in acetonitrile (5 mL) at 75 °C for 2 h, followed by treatment with 0.3 M sulfuric acid in acetonitrile (1 mL) at room temperature. The reaction solution was evaporated and then treated with acetic anhydride (10 mmol) containing pyridine (50 mg) under reflux for 2 h to convert the resulting hydroxyl benzenes into

Keywords: Aerobic oxidation; 1,3,5-Triisopropylbenzene; Hydroperoxide; *N*-hydroxyphthalimide.

^{*} Corresponding author. Tel.: +81 6 6368 0793; fax: +81 6 6339 4026; e-mail: ishii@ipcku.kansai-u.ac.jp

^{0040–4020/\$ -} see front matter @ 2005 Elsevier Ltd. All rights reserved. doi:10.1016/j.tet.2005.08.087

Entry	Temperature/°C	Time/h	Conversion/%	Yield/% ^b		
				2	3	4
1	75	2	78	52 (67)	15 (19)	1 (1.3)
2^{c}	75	5	85	45 (53)	30 (35)	1 (1.1)
3	75	7	96	30 (31)	52 (55)	2 (2.1)
4 ^d	75	5	63	51 (81)	11 (17)	nd
5	65	3	71	51 (73)	17 (24)	nd
6	65	5	84	47 (56)	29 (35)	2 (2.4)
7 ^e	75	2	30	25 (83)	3 (10)	nd
8 ^f	75	2	nr			

Table 1. Aerobic oxidation of 1,3,5-triisopropylbenzene (1) by NHPI under various conditions^a

^a Compound 1 (3 mmol) was reacted in the presence of NHPI (10 mol%) and AIBN (3 mol%) under O_2 (1 atm) in CH₃CN (5 mL). See text. ^b Numbers in parenthesis show selectivity based on 1 reacted.

^c CH₃CN (10 mL).

^d O₂/N₂ (0.5 atm/0.5 atm).

^e Without AIBN.

^f Without NHPI.

WITHOUT NEEDI

acetoxybenzene derivatives whose quantities are determined by GC measurement. As an example, the reaction step of this transformation of 1 to 1,3,5-triacetoxybenzene derivative is shown in Scheme 1. Thus, the amount of phenol derivatives obtained by the oxidation of 1 was estimated as the amount of acetoxybenzene derivatives.



Scheme 1. Sequential transformation of 1 to 4.

The oxidation of **1** followed by above treatment led to 3,5diisopropyl-1-acetoxybenzene (**2**) (52%), 3-isopropyl-1,5diacetoxybenzene (**3**) (15%), and 1,3,5-triacetoxybenzene (**4**) (1%) along with small amounts of decomposed oxidation products like 1-isopropenyl-3,5-diisopropylbenzene (**5**) and 1-acetoxy-3,5- diisopropylbenzene (**6**) at 78% conversion (entry 1).The reaction in acetonitrile (10 mL) for 5 h gave **2** and **3** in 45 and 30% yields, respectively, along with **4** (1%) at 85% conversion (entry 2). Elongation of the reaction time for 7 h under these conditions resulted in the preferential formation of diacetate **3** (52%) over monoacetate **2** (30%) (entry 3). When oxygen concentration was halved under these conditions, **2** was formed in 51% at higher selectivity (81%) (entry 4). The reaction took place smoothly even at 65 °C, affording **2** (51%) and **3** (17%) for 3 h and **2** (47%) and **3** (29%) for 5 h (entries 5 and 6). The reaction in the absence of AIBN led to **2** and **3** in lower yields, and no reaction took place at all in the absence of NHPI (entries 7 and 8).

To inspect suitable solvents to convert **1** into **2**, **3**, and **4**, the effect of several solvents was studied under O_2 (1 atm) at 75 °C for 2 and 5 h (Table 2).

The solvent effect was clearly observed in shorter-time reactions. For example, the oxidation of 1 for 2 h gave rise to 2 (52%) and 3 (15%) at higher conversion (78%) in CH₃CN, but the oxidation in AcOEt afforded 2 (36%) and 3 (6%) at low conversion (42%), although the selectivity of 2 was high (86%) (entries 1 and 2). In the oxidation for 5 h, however, the conversion of 1 was attained up to over 90% in both solvents. On the contrary, the conversions of the oxidations in PhCN and PhCF₃ for 2 h were low compared with that in CH₃CN, but the total selectivities of 2 and 3 of the reaction in both solvents were very high (entries 3 and 4). Acetic acid, which is a good solvent in the NHPIcatalyzed oxidation of toluene to benzoic acid,⁷ was not suited for the present oxidation, since a part of the resulting hydroperoxides was subject to decomposition by acetic acid to form phenols, which serve as radical inhibitors. In fact,

Table 2. Aerobic oxidation of 1,3,5-triisopropylbenzene (1) by NHPI under several solvents^a

Entry	Solvent	Time/h	Conversion/%	Yield/% ^b		
				2	3	4
1	CH ₃ CN	2	78	52 (67)	15 (19)	1 (1.2)
		5	96	29 (30)	51 (53)	2 (2.1)
2	AcOEt	2	42	36 (86)	6 (14)	nd
		5	92	31 (34)	44 (48)	1 (1.1)
3	PhCN	2	66	42 (64)	22 (33)	nd
		5	76	46 (61)	28 (37)	nd
4	PhCF ₃	2	55	36 (65)	16 (29)	1 (1.8)
	-	5	81	33 (41)	36 (44)	1 (1.2)
5	AcOH	2	25	24 (96)	1 (4.0)	nd
		5	30	25 (83)	3 (10)	nd

^a Compound 1 (3 mmol) was reacted in the presence of NHPI (10 mol%) and AIBN (3 mol%) under O_2 (1 atm) in solvent (5 mL) for 2 or 5 h at 75 °C. ^b Numbers in parenthesis show selectivity based on 1 reacted.

the conversion in the oxidation of 1 for 2 h was almost the same as that for 5 h (entry 5). This fact indicates that the oxidation in acetic acid is inhibited at an early stage of the reaction owing to the formation phenols. On the basis of these results, acetonitrile is thought to be a good solvent for the oxidation of 1 from viewpoints of the reaction rate and selectivity among the solvents examined.

In order to obtain further insight into the reaction course, the time-dependence of the oxidation of **1** by the NHPI/AIBN system under O_2 (1 atm) in acetonitrile at 75 °C was followed by GC at an appropriate time interval (Figure 1).



Figure 1. Time-dependence curves for the oxidation of 1 (3 mmol) under O_2 (1 atm) by NHPI (10 mol%) and AIBN (3 mol%) in CH₃CN (5 mL) at 75 °C.

Compound 1 was almost linearly oxidized in 2 h under these conditions to give 2, and 3 with higher selectivity, and the yield of 2 attained maximum (50%) after 2 h. A slightly rapid increase of 3 was observed with the elapse of 1.5 h, but the yield of 3 was not increased beyond 50% and the reaction was stopped at around 6 h. From the consideration of the time-dependence curves of 1, 2, and 3, the reactivity of 2 is thought to be slightly decreased by introduction of OOH group to 1 than that of the stating 1. However, the difficulty of the formation of 4 is believed to be other reasons rather than decrease of the reactivity of 3 by two OOH groups as discussed later.

In order to clarify the reason why the oxidation is stopped at around 6 h, the recovery of NHPI catalyst after the oxidation was examined. Most of the NHPI was found to be recovered without decomposition after 6 h. This fact indicates that the termination of the reaction is not due to the decomposition of NHPI in the course of the oxidation. Consequently, it is reasonable to assume the formation of phenol derivatives, which inhibit the radical chain transfer. It is well known that hydroperoxides undergo the rapid self-decomposition when their concentration increases over the boundary concentration. In fact, we confirmed the formation of 5-isopropyl resorcinol (2%) in the oxidation of 1 with O₂ (1 atm) in the presence of NHPI (10 mol%) and AIBN (3 mol%) in acetonitrile at 75 °C for 6 h. These phenol derivatives generated during the reaction is increased with time and inhibited the further oxidation of 1 to 3 and 4. As a result, the yield of 1,3,5-triacetoxybenzene 4 was not increased with time.

To achieve the reaction at lower temperature, the reaction was carried out under several conditions (Table 3).

The oxidation of **1** was examined using *t*-butylperoxypivarate (BPP), which decomposes at lower temperature $(t_{\frac{1}{2}} = 10 \text{ h at } 55 \text{ °C in benzene) than AIBN } (t_{\frac{1}{2}} = 10 \text{ h at}$ 65 °C in toluene), in CH₃CN at 50 °C for 6 h.⁸ It was found that 1 is selectively converted into 2 (48%) and 3 (27%) at 81% conversion (entry 1). In the oxidation at lower temperature, 4 was not formed at all. By the oxidation using AIBN at 50 °C, the conversion was only 38%, but 2 was selectively produced (entry 2). In a previous paper, we showed that Co(II) reacts with dioxygen to generate a Co(III)-dioxygen complex, which can initiate the NHPIcatalyzed oxidation.⁷ Thus, the oxidation of 1 by NHPI combined with Co(OAc)₂ in place of radical initiators like AIBN and BPP was examined at 50 °C for 1 h. The oxidation was also induced by the NHPI/Co(OAc)₂ to give 2 in high selectivity (91%) in moderate conversion (44%) (entry 3), but the formation of **3**, and **4** was very low. When the reaction time was prolonged to 6 h, the conversion was increased to 95% to lead to 3 (52%) in preference to 2 (34%). High total selectivity of 2, and 3 indicates that the resulting hydroperoxides are relatively stable and do not undergo rapid decomposition by Co ions under these conditions. In contrast, since Cu ions promote the redox decomposition of hydroperoxides, the oxidation of 1 using the NHPI/Cu(OAc)₂ system resulted in a complex mixture compared with that of the NHPI/Co(OAc)₂ system probably because of side reactions caused by decomposition of the resulting hydroperoxides by Cu ions (entry 6).

Figure 2 shows the time-dependence curves for the oxidation of **1** by NHPI combined with BPP or AIBN at 50 °C. The reaction by the NHPI/AIBN system proceeded more slowly than that by the NHPI/BPP system owing to the difficulty of the decomposition of AIBN at 50 °C. After

Table 3. Aerobic oxidation of 1,3,5-triisopropylbenzene (1) by NHPI at 50 °C in the presence of various initiators^a

Entry	Initiator (mol%)	Time/h	Conversion/%	Yield/% ^b			
				2	3	4	
1	BPP (3)	6	81	48 (59)	27 (33)	nd	
2	AIBN (3)	6	38	37 (97)	1 (2.6)	nd	
3	$Co(OAc)_2$ (0.1)	1	44	40 (91)	1 (2.6)	1 (1.2)	
4	$Co(OAc)_{2}(0.1)$	6	95	34 (36)	52 (55)	2 (2.1)	
5	$Cu(OAc)_{2}(0.1)$	1	55	41 (81)	7 (13)	nd	
6	$Cu(OAc)_2(0.1)$	6	Complex mixture				

^a Compound 1 (3 mmol) was reacted in the presence of NHPI (10 mol%) and radical initiator under O_2 (1 atm) in CH₃CN (5 mL) at 50 °C for 1 or 6 h. ^b Numbers in parenthesis show selectivity based on 1 reacted.



NHPI / AIBN

Figure 2. Time-dependence curves for aerobic oxidation of 1 (3 mmol) under O_2 (1 atm) by NHPI (10 mol%)/AIBN (3 mol%) or NHPI (10 mol%)/BPP (3 mol%) in CH₃CN (5 mL) at 50 °C.

15 h, the yields of 2, 3, and 4 in the oxidation of 1 by the NHPI/BPP system attained 40, 58, and 1% yields, respectively, while in the oxidation by the NHPI/AIBN system the starting 1 was remained even after 15 h. These observations suggest that the NHPI/BPP system is more efficient than the NHPI/AIBN one in the oxidation of 1 to 2, and 3 at 50 °C.

Since it was difficult to obtain 1,3,5-triacetoxybenzene 4 by the oxidation of 1 under O_2 (1 atm), the oxidation of 1 under pressurized air (30 atm) was carried out by use of the NHPI/ AIBN system at 75 °C for 24 h (Eq. 2).



The reaction afforded 4 in 21% yield along with 3 (54%) and 2 (10%), although 4 was difficult to obtain selectively. The

fact that the yield of **4** by the oxidation of **1** with air was increased compared with that with pure oxygen is believed to be due to the slower formation of phenol derivatives, which serve as radical inhibitor, with air than that with O_2 .

In conclusion, we have first examined the aerobic oxidation of 1 to obtain polyphenols by the use of combined catalytic system of NHPI with a radical initiator like AIBN or BPP. The NHPI/AIBN system was found to be a good system for the oxidation of 1 to 2, and 3, and the NHPI/BPP system showed high performance for the oxidation of 1 at lower temperature. The oxidation of 1 by NHPI in the presence of AIBN under pressurized air (30 atm) followed by above treatment led to 1,3,5-triacetoxybenzene 4 in fair yield (21%).

3. Experimental

3.1. General procedure

¹H NMR and ¹³C NMR were measured at 270 and 67.5 MHz, respectively, in CDCl₃ with TMS as the internal standard. Infrared (IR) spectra were measured as thin films on NaCl plate or KBr press disk. A GLC analysis was performed with a flame ionization detector using a 0.2 mm \times 25 m capillary column (OV-17). Mass spectra were determined at an ionizing voltage of 70 eV. All starting materials, catalysts, and initiators were purchased from commercial sources and used without further treatment. The yields of products were estimated from the peak areas based on the internal standard technique.

3.2. General procedure for the oxidation of 1,3,5triisopropylbezene (1) to acetoxylbenzene derivatives, 2, 3, and 4

An acetonitrile (5 mL) solution of 1,3,5-triisopropylbenzene (1) (3 mmol), AIBN (3 mol%), and NHPI (10 mol%) was placed in a two-necked flask equipped with a balloon filled with O₂, and the solution was stirred at 75 °C for 2–7 h. The reactant was treated with 0.3 M H₂SO₄ in CH₃CN (1 mL) at 25 °C for 2 h. In this reaction, the resulting hydroperoxides are conformed to be converted into phenol derivatives and acetone by GC-MS measurement. After removal of solvent under reduced pressure, the mixture was treated with acetic anhydride (10 mmol) containing pyridine (50 mg) under reflux for 1 h to covert into acetoxybenzene derivatives whose quantities are determined by GC measurement. The resulting products were purified by column chromatography on silica gel using n-hexane to give 5-acetoxy-1,3diisopropylbenzene (2), 3,5-diacetoxy-1-isopropylbenzene (3), 1,3,5-triacetoxybenzene (4). These products were characterized by 1 H and 13 C NMR, IR, and HRMS, respectively.

3.2.1. 5-Acetoxy-1,3-diisopropylbenzene (2). ¹H NMR δ 6.94 ppm (s, 1H), 6.75 ppm (d, J = 1.4 Hz, 2H), 2.91–2.83 ppm (m, 2H), 2.28 ppm (s, 3H), 1.23 ppm (d, J = 6.9 Hz, 12H); ¹³C NMR 169.4, 150.6, 150.1, 122.3, 116.7, 34.1, 24.0, 21.2; IR(NaCl) 2961, 2871, 1768, 1458, 1207, 872, 704 cm⁻¹; HRMS (EI): calcd for C₁₄H₂₀O₂ [M-H]⁺: 220.1436; found: 220.1463.

3.2.2. 3,5-Diacetoxy-1-isopropylbenzene (3). ¹H NMR δ , 6.78 ppm (q, J=2.4 Hz, 2H), 6.74 ppm (s, 1H) 2.91–2.88 ppm (m, 1H), 2.28 ppm (s, 3H), 1.23 ppm (d, J= 6.9 Hz, 6H); ¹³C NMR 169.1, 151.3, 150.8, 117.0, 112.7, 33.9, 23.6, 21.1; IR(NaCl) 2956, 2871, 1771, 1455, 1198, 891, 707 cm⁻¹; HRMS (EI): calcd for C₁₃H₁₆O₄ [M-H]⁺: 236.1051; found: 236.1049.

3.2.3. 1,3,5-Triacetoxybenzene (4). ¹H NMR δ 6.83 ppm (s, 3H), 2.27 ppm (2, 9H); ¹³C NMR 168.4, 151.0, 21.2; IR(NaCl) 3091, 1772, 1457, 1189, 918, 670 cm⁻¹; HRMS (EI): calcd for C₁₂H₁₂O₆ [M-H]⁺: 252.0658; found: 252.0634.

Acknowledgements

This work was partially supported by a Grant-in-Aid for Scientific Research on Priority Areas (17065019) from the Ministry of Education, Science and Culture, Culture, Japan, and Daicel Chemical Industries Ltd.

References and notes

1. (a) Park, C.; Sheehan, J. R. In *Kirk-Othmer Encyclopedia of Chemical Technology*, 4th ed.; Wiley: New York, Vol. 18W,

1996. (b) Partenheimer, W. *Catal. Today* **1995**, *23*, 69. (c) Parshall, G. W.; Ittel, S. D. *Heterogeneous Catalysis*, 2nd ed.; Wiley: New York, 1992.

- (a) Hock, H.; Lang, S. *Ber. Dtsch. Chem. Ges.* **1944**, *B77*, 257.
 (b) Jordan, W.; Van Barneveld, H.; Gerlich, O.; Boymann, M. K.; Ullrich, J.; Ullmann's Encyclopedia of Industrial Organic Chemicals; Wiley-VCH: Weinheim, 1985; Vol. A9; pp 299–312.
- (a) Wessermel, K.; Arpe, H.-J. Industrial Organic Chemistry.; Wiley-VCH: Weinheim, 2003; pp 364–366.(b) Ching Y. W. Eur. Patent 322245, 1989.
- 4. Fukuda, O.; Sakaguchi, S.; Ishii, Y. Adv. Synth. Catal. 2001, 343, 809.
- (a) Aoki, Y.; Sakaguchi, S.; Ishii, Y. *Tetrahedron* 2005, 61, 5219.
 (b) Aoki, Y.; Sakaguchi, S.; Ishii, Y. *Adv. Synth. Catal.* 2001, 346, 199.
 (c) Arends, I. W. C. E.; Sasiidharan, M.; Kuhnle, A.; Duda, M.; Jost, C.; Sheldon, R. A. *Tetrahedron* 2002, 58, 9055.
- (a) Ogino, T. JP 03044344, 1991. (b) Mizuno, K. JP 61152635, 1986.(c) Reichle, W. T.; Konrad, F. M.; Brooks, J. R. *Benzene and its Industrial Derivatives*; Benn: London, 1975.
- Yoshino, Y.; Hayashi, Y.; Sakaguchi, S.; Ishii, Y. J. Org. Chem. 1997, 62, 6810.
- It has been reported that the self-accelerating decomposition temperatures of AIBN and BPP were 50.0 and 27.0 °C, respectively; Bosch, C. M.; Velo, E.; Recasens, F. *Chem. Eng. Sci.* 2001, 56, 1451.