JOC *Article*

Oxidation of Substituted Toluenes with Molecular Oxygen in the Presence of *N*,*N*′,*N*″-Trihydroxyisocyanuric Acid as a Key Catalyst

Naruhisa Hirai,[†] Naoko Sawatari,[‡] Norihiro Nakamura,[‡] Satoshi Sakaguchi,[‡] and Yasutaka Ishii*,[‡]

Daicel Chemical Industry, Ltd., Shinzaike, Aboshi-ku, Himeji Hyogo 671-1283, and Department of Applied Chemistry & High Technology Research Center, Faculty of Engineering, Kansai University, Suita, Osaka 564-8680, Japan

ishii@ipcku.kansai-u.ac.jp

Received March 10, 2003

N,*N*′,*N*″-Trihydroxyisocianuric acid (THICA) was found to be a very efficient catalyst for the oxidation of alkylbenzenes with dioxygen. Thus, a variety of meta- and para-substituted toluenes bearing an electron-withdrawing substituent such as cyanotoluene, chlorotoluene, and toluic acid under O_2 (1 atm) in the presence of THICA (5 mol %) and $Co(OAc)_2$ (0.5 mol %) at 100 °C were smoothly oxidized to the corresponding benzoic acids in almost quantitative yields. The aerobic oxidation of toluene by THICA was compared with that by *N*-hydroxyphthalimide. *p*-Xylene was efficiently oxidized by THICA to telephthalic acid in high yield (over 95%) under mild conditions.

Introduction

Aerobic oxidation of alkylbenzenes is a very important process in industrial chemistry and is currently carried out in large scale. These aerobic oxidations, which are usually called autoxidation, are practiced under the influence of a small amount of cobalt and manganese salts in the presence of bromine at higher temperature.[1] In particular, conversion of *p*-xylene to telephthalic acid, which is an important polymer material for PET resin, is one of the most important industrial oxidation processes. We have recently developed an innovative catalytic method for aerobic oxidation of alkanes using *N*-hydroxyphthalimide (NHPI), which serves as a *carbon radical producing catalyst* (CRPC) from alkanes.[2] Thus, alkanes such as ethane, isobutene, cyclohexane, and alkylbenzenes can be efficiently oxidized with dioxygen to oxygen-containing compounds such as alcohols, ketones, and carboxylic acids under mild conditions. In the oxidation of alkanes with O_2 by NHPI combined with Co(II), the key step of the oxidation is the generation of a phthalimide *N*-oxyl (PINO) radical, which possesses a strong electrophlic property, from the NHPI by a cobalt(III)−oxygen complex generated in situ from Co(II) and molecular oxygen. The resulting PINO abstracts the hydrogen atom from the C−H bond of alkanes to lead to alkyl radicals which are readily trapped by O_2 to give eventually oxygen-containing products through the redox decomposition of alkyl hydroperoxides.[3] NHPI as the CRPC is very unique and deserves attention as a new catalyst for generation of carbon radicals from various compounds such as alkanes, alkenes, alkynes, alcohols, ethers, etc. The novel catalytic behavior of NHPI prompted us to investigate a new class of CRPCs which are capable of generating carbon radicals from C−H bonds, other than the NHPI analogues. In the course of our study to obtain a new CRPC, we have found that *N*,*N*′,*N*″-trihydroxyisocianuric acid (THICA) serves as a good CRPC from alkylbenzenes. In this paper, we have disclosed aerobic oxidations of various substituted toluenes employing THICA as a key catalyst.

Results and Discussion

The oxidation of toluene (**1**) with dioxygen by THICA in acetic acid under several reaction conditions was examined and compared with that by NHPI (eq 1, Table 1).

It was found that **1** was oxidized with dioxygen (1 atm) in the presence of only 1 mol % THICA and 0.5 mol % $Co(OAc)_2$ at 80 °C for 6 h to give benzoic acid (**2**) (68%) along with a small amount of benzaldehyde (**3**) (3%) (run 1). This indicates that THICA serves efficiently as a CRPC from **1**. Under the same conditions using 1 mol % NHPI, **1** was only converted to **2** in lower yield (20%) (run 2). Even by the use of 3 mol % NHPI in this oxidation, the yield (47%) of **2** was lower than that by the use of 1 mol % THICA (run 3). These results show that THICA is more effective than NHPI for the oxidation of **1**. When 3 mol % THICA was used under these conditions, **1** was oxidized to **2** in high yield (93%) (run 4). In the oxidation

---

[†] Daicel Chemical Industry, Inc.

[‡] Kansai University.

(1) (a) Parshall, G. W.; Ittel, S. D. *Homogeneous Catalysis*, 2nd ed.; Wiley: New York, 1992; p 225. (b) Park, C. J.; Sheehan, R. In *Kirk-Othmer Encyclopedia of Chemical Technology*, 4th ed.; Kroschwite, J. I., Howe-Grant, M., Eds.; John Wiley and Sons: New York, 1996; Vol. 18, p 991. (c) Sheehan, J. R. In *Ullmann's Encyclopedia Industrial Organic Chemicals*; Ullmann, F., Ed.; Wiley-VCH: Weinheim, Germany, 1999; Vol. 8, p 4575. (d) Partenheimer, W. *Catal. Today* **1995**, *23*, 69.

(2) Ishii, Y.; Sakaguchi, S.; Iwahama, T. *Adv. Synth. Catal.* **2001**, *343*, 393.

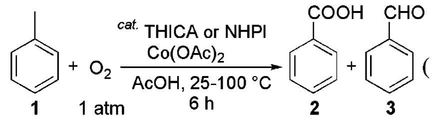
(3) Yoshino, Y.; Hayashi, Y.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* **1997**, *62*, 6810.

10.1021/jo034313z CCC: $25.00

TABLE 1. Oxidation of 1 with O_2 (1 atm) by NHPI and THICA under Various Conditions[a]

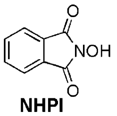
run	catalyst (mol %)	temp (°C)	conversn (%)	yield (%)	
				2	**3**
1	THICA (1)	80	71	68	3
2	NHPI (1)	80	25	20	5
3	NHPI (3)	80	53	47	3
4	THICA (3)	80	>99	93	2
5	THICA (5)	80	>99	>99	nd
6	THICA (3)	100	>99	>99	nd
7[b]	THICA (5)	25	1	nd	trace
8[b]	NHPI (5)	25	39	34	5

[a] **1** (3 mmol) was reacted under O_2 (1 atm) in the presence of THICA or NHPI and $Co(OAc)_2$ (0.5 mol %) in AcOH (5 mL) at 25−100 °C for 6 h. [b] 20 h.

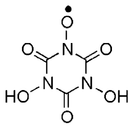


(1)

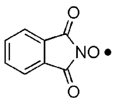
THICA



NHPI



A



PINO

of **1** at room temperature by THICA and NHPI, however, **1** was gradually oxidized to **2** by NHPI, but no oxidation was observed when THICA was used. In a previous paper on the oxidation of **1** to **2** with O_2 by NHPI combined with Co(II) at room temperature, we showed that the oxidation is initiated by the hydrogen atom abstraction from the hydroxyimide group in NHPI by a cobalt(III)−oxygen complex to form a PINO radical.[3] Since the oxidation by THICA is considered to proceed by a reaction path similar to that of the oxidation by NHPI, the fact that no oxidation was observed by THICA at room temperature indicates that the hydrogen atom abstraction from the hydroxyimide moiety of THICA by the Co(III)−oxygen complex has difficulty taking place at up to 25 °C. Minsci et al. have reported that the O−H bond dissociation energy of NHPI is evaluated as 88.1 kcal/mol.[4] Our ab initio calculation for the O−H bond dissociation energy for THICA and NHPI was 91.6 and 88.1 kcal/mol, respectively.[5] These results show that a higher temperature is needed for the generation of an *N*-oxyl radical (**A**) from THICA than from NHPI. Therefore, the oxidation by THICA has difficulty taking place at room temperature.

On the basis of these results, a variety of substituted toluenes were allowed to react under O_2 in the presence of THICA combined with $Co(OAc)_2$ (Table 2).

Although alkylbenzenes substituted by electron-withdrawing groups are reluctant to be oxidized with O_2, *p*-cyanotoluene (**4**) oxidized by THICA under 1 atm of O_2 at 100 °C for 6 h was completely converted into *p*-cyanobenzoic acid (**5**), which is an important pharmaceutical precursor (run 1).[6] The same oxidation by NHPI led to **5** in somewhat lower yield (79%) (run 2). Because of the difficulty in converting **4** to **5** by aerobic oxidation so far, liquid-phase oxidation by CrO_3 with H_2SO_4 in acetic acid[7] or by NaOCl with H_2SO_4 in the presence of $RuCl_3$ catalyst under phase-transfer conditions was employed for the production of **5**.[8] Therefore, this is the first successful aerobic oxidation of **4** to **5**. *p*-Methoxytoluene (**6**), *p*-chlorotoluene (**8**), and *p*-bromotoluene (**10**) were also oxidized to the corresponding carboxylic acids **7**, **9**, and **11** in good to excellent yields, respectively (runs 3−5). It is reported that the aerobic oxidation of **8** by an immobilized Co(III) catalyst at 130 °C gave **9** in only 25% yield.[9] Therefore, the present method provides a good route to **9**. *p*-Toluic acid (*p*-**12**) was also completely converted into telephthalic acid (*p*-**13**), which is a very important monomer for PET resin and fiber (runs 6 and 7). We next tried the aerobic oxidation of acetoxytoluenes **14** by both THICA and NHPI (runs 8 and 9). *p*-Acetoxytoluene (*p*-**14**) is reported to be oxidized to *p*-acetoxybenzoic acid (*p*-**15**) in 50% yield with hydrogen peroxide catalyzed by $RuCl_3$ on montmorillonite.[10] The oxidation of *m*- and *p*-**14** by THICA proceeded in relatively good yields, but *o*-acetoxytoluene (*o*-**14**) was a reluctant substrate for the oxidation to give the corresponding acid *o*-**15** in very low yield (5.3%) (runs 8−12). Hence, the oxidation of *o*-**14** was carried out at 150 °C, but the yield of *o*-**15** was no more than 9% (run 13). Nitrotoluenes **16** having a strong electron-withdrawing substituent showed a behavior similar to that of acetoxytoluenes **14**. THICA efficiently catalyzed the oxidation of *p*- and *m*-**16** to form *p*- and *m*-nitrobenzoic acids (*p*- and *m*-**17**) in good yields (runs 14 and 15). Since THICA is more stable than NHPI at higher temperature, *o*-**16** could be oxidized at 150 °C to give *o*-**17** in fair yield (62%) (runs 16 and 17). However, the same oxidation using NHPI instead of THICA gave 46% yield probably because of the decomposition of NHPI. On the other hand, toluenes substituted by an electron-donating group such as *p*-*tert*-butyltoluene (**18**) were easily oxidized to acids such as *p*-*tert*-butylbenzoic acid (**19**) in quantitative yield (run 18). Unfortunately, *p*-ethyltoluene (**20**) was difficult to oxidize selectively to *p*-methylacetophenone (**21**) (run 19).

It is interesting to compare the time-dependence curves for the aerobic oxidation of *p*-xylene (*p*-**22**) to *p*-**12** and *p*-**13** by using THICA (3 mol %) and NHPI (10 mol %) combined with $Co(OAc)_2$ (0.5 mol %) and $Mn(OAc)_2$ (0.5 mol %) in acetic acid at 100 °C (Figures 1 and 2).

Despite the fact that the oxidation of *p*-**22** by NHPI occurred very fast up to the formation of a 65% yield of *p*-**12**, the reaction stopped at this stage as shown in Figure 2. This is believed to be due to the deactivation of NHPI by decomposition. In contrast, the oxidation of *p*-**22** by THICA gave *p*-**12**, which then undergoes further

---

[4] Amorati, R.; Lucarini, M.; Mugnaini, V.; Pedulli, G. F.; Minisci, F.; Recupero, F.; Fontana, F.; Astolfi, P.; Greci, L. *J. Org. Chem.* **2003**, *68*, 1747.

[5] The O−H bond dissociation energy of THICA and NHPI was calculated using the PMP2/6-31++G**//HF/6-31G** level of theory.

[6] (a) Robertson, D. W.; Krushinski, J. H.; Beedle, E. E. *J. Med. Chem.* **1987**, *30*, 552. (b) Koyama, M.; Ohtani, N.; Fumio, K. *J. Med. Chem.* **1985**, *28*, 717.

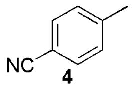
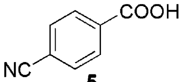
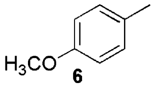
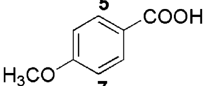
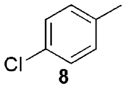
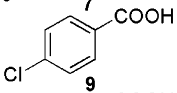
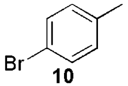
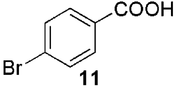
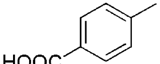
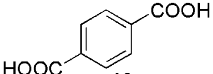
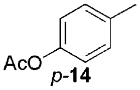
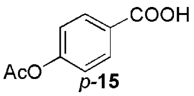
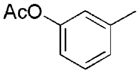
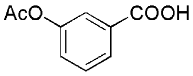
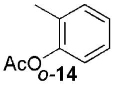
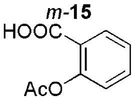
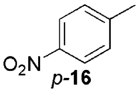
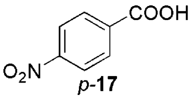
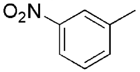
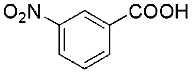
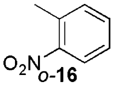
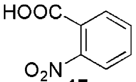
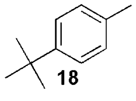
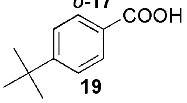
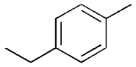
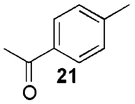
[7] Levine, M.; Sedlecky, R. *J. Org. Chem.* **1959**, *24*, 115.

[8] Sasson, Y.; Zappi, G. D.; Neuman, R. *J. Org. Chem.* **1986**, *51*, 2880.

[9] Das, B. K.; Clark, J. H. *Chem. Commun.* **2000**, 605.

[10] Milind, D.; Sudalai, A. *Tetrahedron* **1999**, *55*, 5903.

TABLE 2. Oxidation of Substituted Toluenes with O_2 (1 atm) by THICA and NHPI Combined with $Co(OAc)_2$[a]

Run	Substrate	Catalyst (mol%)	Time (h)	Temp. (°C)	Conv. (%)	Product	(Yield / %)
1	 **4**	THICA (5)	6	100	>99	 **5**	(>99)
2		NHPI (10)	14	100	>99		(79)
3	 **6**	THICA (3)	6	80	>99	 **7**	(>99)
4	 **8**	THICA (5)	14	100	>99	 **9**	(>99)
5	 **10**	THICA (3)	6	100	>99	 **11**	(>99)
6	 ***p*-12**	THICA (5)	6	100	>99	 ***p*-13**	(>99)
7		NHPI (10)	14	100	93		(88)
8[b]	 ***p*-14**	THICA (5)	6	100	85	 ***p*-15**	(74)
9[b]		NHPI (10)	14	100	62		(53)
10[b]	 ***m*-14**	THICA (5)	14	100	78	 ***m*-15**	(75)
11[b]		NHPI (10)	14	100	59		(53)
12[b]	 ***o*-14**	THICA (5)	14	100	8.6	 ***o*-15**	(5.3)
13[b]		THICA (5)	14	150	14		(9)
14[c]	 ***p*-16**	THICA (5)	14	130	92	 ***p*-17**	(87)
15[c]	 ***m*-16**	THICA (5)	14	100	>99	 ***m*-17**	(88)
16[d]	 ***o*-16**	THICA (5)	14	150	67	 ***o*-17**	(62)
17[d]		NHPI (10)	14	150	52		(46)
18	 **18**	THICA (3)	4	100	>99	 **19**	(>99)
19	 **20**	THICA (3)	6	100	>99	 **21**	(60)[e]

[a] Substrate (3 mmol) was reacted under O_2 (1 atm) in the presence of THICA or NHPI and $Co(OAc)_2$ (0.5 mol %) in AcOH (5 mL). [b] AIBN (1 mol %) and $Mn(OAc)_2$ (0.05 mol %) were added. [c] $Mn(OAc)_2$ (0.05 mol %) was added. [d] NO_2 (20 mol %) and $Mn(OAc)_2$ (0.05 mol %) were added. [e] 4-Acetylbenzoic acid (24%), *p*-**12** (3%), and *p*-**13** (5%) were also obtained.

oxidation to form *p*-**13** in good yield. These results may indicate that the character of the *N*-oxyl radical PINO generated from NHPI is different from that of the *N*-oxyl radical **A** derived from THICA. From consideration of these two time-dependence curves, it is apparent that PINO is a more reactive radical species than **A**. As a result, the former radical is easily decomposed compared to the latter during the oxidation of *p*-**22**. In fact, the GC analysis of the reactants after the oxidation of *p*-**22** by NHPI shows the formation of phthalimide and phthalic anhydride resulting from the N−O bond cleavage of NHPI. Owing to the complexity of the reaction process in the chain reaction, it is difficult to explain why the phthalimide is formed in the oxidation of *p*-**22** by NHPI. However, it seems to be related to the violent propagation step in the oxidation of *p*-**22**, which is a reactive substrate for aerobic oxidation.

Experimental Section

Starting materials and catalysts were purchased from commercial sources and used without further treatment. Yields were estimated from the peak areas on the basis of the internal standard technique by using GC. GC analysis was performed with a flame ionization detector using a 0.2 mm × 30 m capillary column. ^1H and ^{13}C NMR spectra were measured at 270 and 68 MHz, respectively, in chloroform-*d* with Me_4Si as the internal standard. Infrared (IR) spectra were measured using NaCl or KBr pellets. GC−MS spectra were obtained at

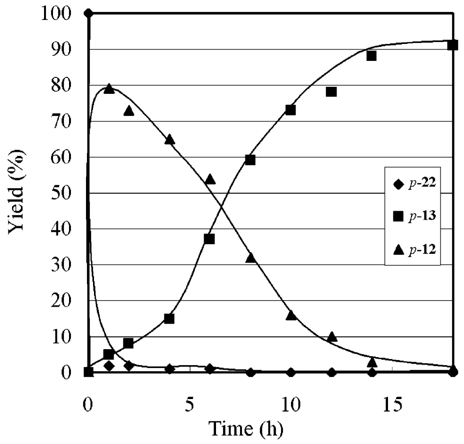


FIGURE 1. Time-dependence curves for aerobic oxidation of *p*-**22** to *p*-**12** and *p*-**13** under O_2 (1 atm) in the presence of THICA (3 mol %) combined with $Co(OAc)_2$ (0.5 mol %) and $Mn(OAc)_2$ (0.5 mol %).

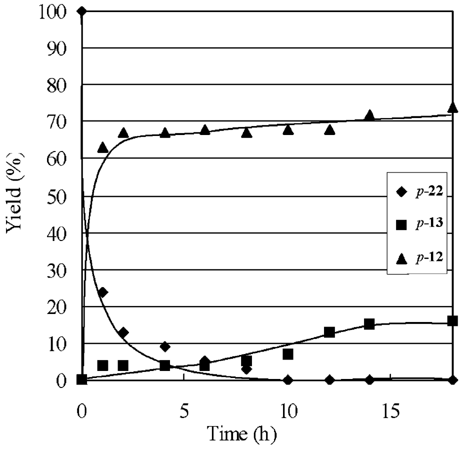


FIGURE 2. Time-dependence curves for aerobic oxidation of *p*-**22** to *p*-**12** and *p*-**13** under O_2 (1 atm) in the presence of NHPI (10 mol %) combined with $Co(OAc)_2$ (0.5 mol %) and $Mn(OAc)_2$ (0.5 mol %).

an ionization energy of 70 eV. All products were known compounds and were identified by comparison of the isolated products with authentic samples.

Preparation of *N*,*N*′,N″-Trihydroxyisocyanuric Acid. THICA was prepared by a modified literature procedure.[11] 1,1′-Carbonyldiimidazole (165 mmol) was added to a pyridine (250 mL) solution of *O*-benzylhydroxylamine (150 mmol) under Ar. The mixture was stirred for 1 h at room temperature, and then the temperature was increased to 60 °C for 6 h and 90 °C for 5 h. After the reaction, the solvent was removed under reduced pressure until the mixture was 100 g. Water (500 mL) was added slowly to the mixture to give a white precipitate. The precipitate was filtered and washed with water (50 mL), AcOH (40 mL), and *n*-hexane (40 mL). The solid was recrystallized from AcOH (80 mL) and AcOEt (70 mL) and dried under vacuum to give tribenzyloxy-1,3,5-triaine-2,4,6(1*H*,3*H*,5*H*)-trione (TBTA) (5.1 g) in 23% yield:

^1H NMR (DMSO-d_6/TMS) δ 7.52 (m, 2H), 7.42 (m, 3H), 5.10 (s, 2H); ^{13}C NMR (DMSO-d_6/TMS) δ 144.8, 133.4, 129.5, 129.0, 128.3, 78.4; IR (KBr) 1740(s), 1401(s), 1197(m), 1001(s), 750(s), 696(s) cm^{-1}.

TBTA (5 mmol) in 100 mL of dioxane was hydrogenated on 10 wt % Pd/C (0.5 g) under normal pressure of hydrogen at room temperature overnight. After removal of the catalyst by filtration, the filtrate was evaporated under reduced pressure to afford THICA, which was recrystallized from acetone in 90% yield: ^1H NMR (DMSO-d_6/TMS) δ 11.03 (s, 3H); ^{13}C NMR (DMSO-d_6/TMS) δ 146.6; IR (KBr) 3539(s), 3166(s), 2827(s), 1720(s), 1433(s), 1211(m), 1010(s), 701(s) cm^{-1}. The X-ray analysis of THICA indicates that three OH groups are situated at the same plane.

Oxidation of Substituted Toluenes under a Dioxygen Atmosphere. An acetic acid solution (5 mL) of substrate (3 mmol), THICA, and $Co(OAc)_2$ (0.5 mol %) was paced in a 50 mL pear-shaped flask with a balloon filled with O_2. The mixture was stirred at 25−100 °C for 6 h. After the reaction, the solvent was removed under reduced pressure, and the products were purified by column chromatography on silica gel to give the corresponding oxygenated products. The products were identified through comparison of isolated products with authentic samples.

Acknowledgment. This work was partially support by a Grant-Aid for Scientific Research (KAKENHI) (S) (No. 13853008) from the Japan Society for the Promotion of Science (JSPS).

JO034313Z

---

[11] (a) Butula, I.; Takac, M. *Croat. Chem Acta* **2000**, *2*, 569. (b) Staab, H. A.; Benz, W. *Angew. Chem.* **1961**, *73*, 657.