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# Aerobic oxidation of trimethylbenzenes catalyzed by *N,N',N''*-trihydroxyisocyanuric acid (THICA) as a key catalyst

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**Abstract**—The oxidation of trimethylbenzenes was examined with air or O<sub>2</sub> using *N,N',N''*-trihydroxyisocyanuric acid (THICA) as a key catalyst. Thus, 1,2,3-, 1,2,4-, and 1,3,5-trimethylbenzenes under air (20 atm) in the presence of THICA (5 mol %), Co(OAc)<sub>2</sub> (0.5 mol %), Mn(OAc)<sub>2</sub>, and ZrO(OAc)<sub>2</sub> at 150 °C were oxidized to the corresponding benzenetricarboxylic acids in good yields (81–97%). In the aerobic oxidation of 1,2,4-trimethylbenzene by the THICA/Co(II)/Mn(II) system, remarkable acceleration was observed by adding a very small amount of ZrO(OAc)<sub>2</sub> to the reaction system to form 1,2,4-benzenetricarboxylic acid in excellent yield (97%). In contrast, no considerable addition effect was observed in the oxidation of 1,3,5-trimethylbenzene. This aerobic oxidation by the present catalytic system provides an economical and environmentally benign direct method to benzenetricarboxylic acids, which are very important polymer materials. © 2006 Elsevier Ltd. All rights reserved.

## 1. Introduction

Aromatic tricarboxylic acids like 1,2,3-benzenetricarboxylic acid (hemimellitic acid), 1,2,4-benzenetricarboxylic acid (trimellitic acid), and 1,3,5-benzenetricarboxylic acid (trimesic acid), which are converted into their anhydrides are of industrial importance. These anhydrides are used to make plasticizers for polyvinyl chloride and are also used as monomer materials for polyester and polyimide resins having high thermal resistance. These polycarboxylic acids are produced in large scale by aerobic oxidation of the corresponding trimethylbenzenes or by oxidation with dilute nitric acid (ca. 7%), which is known as the Amoco method<sup>1</sup> or the Bergwerksverband method,<sup>2</sup> respectively. An alternative process for trimellitic acid involves carboxylation of *m*-xylene followed by aerobic oxidation in the presence of MnBr<sub>2</sub>/HBr.<sup>1e,3</sup> The aerobic oxidation is usually carried out under the influence of a small amount of cobalt and manganese salts in the presence of bromine.<sup>1,4</sup> However, the autoxidation of polymethylbenzenes must be carried out under harsh conditions (higher pressure and temperature). In addition, the need of the corrosive bromide ion as a promoter calls for the use of reactors made of titanium alloy. Fortunately, we have recently developed an innovative halogen-free catalytic method for aerobic oxidation of alkanes using *N*-hydroxyphthalimide (NHPI), which serves as a

carbon radical producing catalyst (CRPC) from alkanes.<sup>5</sup> Thus, alkanes like ethane, isobutene, cyclohexane, and alkylbenzenes can be efficiently oxidized with dioxygen to oxygen-containing compounds like alcohols, ketones, and carboxylic acids under mild conditions. In the aerobic oxidation of alkenes by NHPI combined with Co(II), the key step in sequential reactions is the generation of a phthalimide-*N*-oxyl (PINO) radical by the hydrogen abstraction from the NHPI by oxygen or 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 that are readily trapped by O<sub>2</sub> to give eventually oxygen-containing products through the redox decomposition of alkylhydroperoxides by metal ions. The catalysis of NHPI as the CRPC is very unique and deserves attention as a new catalyst for generation of carbon radicals by hydrogen abstraction from various C–H bonds like alkanes, alkenes, alkynes, alcohols, and ethers, etc. In the oxidation of alkylbenzenes like *p*-xylene, which are susceptible to autoxidation, however, the NHPI was found to be converted into an inactive species like phthalimide in the course of the oxidation owing to a violent chain reaction. Hence, the oxidation must be carried out in the presence of a large amount of NHPI (20 mol %) to obtain terephthalic acid in higher yield. In the course of our study to develop an NHPI analogue, which can be stable at higher temperature, we have found *N,N',N''*-trihydroxyisocyanuric acid (THICA), which serves as a good CRPC from alkylbenzenes.<sup>6</sup> In this paper, we wish to report the aerobic oxidation of trimethylbenzenes by THICA as a key catalyst.

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## 2. Results and discussion

The aerobic oxidation of 1,2,4-trimethylbenzene (pseudocumene) (**1**) by THICA in acetic acid under several reaction conditions was first examined (Table 1).

The oxidation of **1** under air (20 atm) in the presence of THICA (5 mol %), Co(OAc)<sub>2</sub> (0.5 mol %), and Mn(OAc)<sub>2</sub> (0.5 mol %) at 120 °C for 6 h afforded a mixture of mono, di, and tricarboxylic acids, **2**, **3**, and **4**, in 10%, 66%, and 7% yields, respectively (entry 1). Although the reaction time was prolonged to 14 h, the yield of desired 1,2,4-benzenetricarboxylic acid (trimellitic acid) **4** was slightly increased (24%) (entry 2). When the amount of Co(OAc)<sub>2</sub> and Mn(OAc)<sub>2</sub> was increased to 2 mol % under these conditions, it was found that the oxidation was considerably accelerated by these metal ions and the main product in the oxidation became trimellitic acid **4** (54%) rather than **3** (31%) (entry 3). The oxidation at higher temperature (150 °C) afforded **4** in high yield (70%) along with **3** (19%) (entry 4), although the oxidation using NHPI is difficult to carry out at 150 °C because of decomposition under such circumstances. It is interesting to note that a small amount of ZrO(OAc)<sub>2</sub> (0.5 mol %) was added to the catalytic system to lead to **4** in an almost quantitative yield (97%) (entry 5). The acceleration effect of the Zr additive on the Co-catalyzed autoxidation has appeared in a patent by Ichikawa.<sup>4a</sup> Subsequently, the effect of a Zr species on the Co/Mn/Br system was studied in detail by Partenheimer<sup>4b</sup> who pointed out the importance of Lewis acidity of the Zr species in the oxidation of *p*-xylene. There is no systematic study on the aerobic oxidation of **1** in the literature except for several patent works. In these patents, the aerobic oxidations of **1** by the Co/Mn/Br/Zr system was carried out under 10–27 atm of air at 160–210 °C to lead to trimellitic acid **4** in about 90% yield.<sup>4c</sup> Therefore, it is

**Table 1.** Aerobic oxidation of 1,2,4-trimethylbenzene (**1**) by THICA under selected conditions<sup>a</sup>

Entry	Co(II)/Mn(II) (mol %)	Temp (°C)	Time (h)	Yield (%) <sup>b</sup>		
				2	3	4
1	0.5/0.5	120	6	10	66	7
2	0.5/0.5	120	14	Trace	68	24
3	2/2	120	6	n.d.	31	54
4	2/2	150	6	n.d.	19	70
5 <sup>c</sup>	0.5/0.5	150	6	n.d.	n.d.	97

<sup>a</sup> Compound **1** (1 mmol) was oxidized under air (20 atm) in the presence of THICA (5 mol %), Co(OAc)<sub>2</sub>·4H<sub>2</sub>O, and Mn(OAc)<sub>2</sub>·4H<sub>2</sub>O in AcOH (2.5 mL).

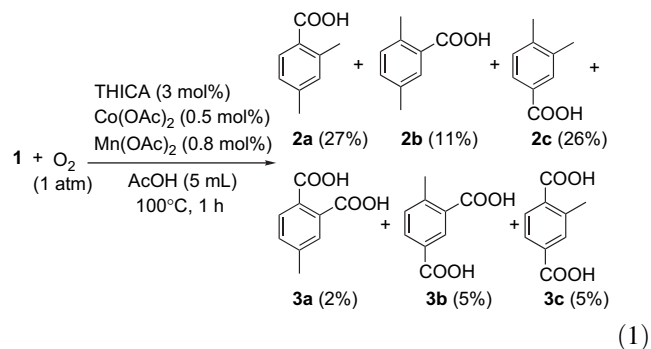
<sup>b</sup> Conversion of **1** was over 99% in each run.

<sup>c</sup> ZrO(OAc)<sub>2</sub> (0.5 mol %) was added.

important to note that the oxidation of **1**, which has been difficult to carry out up to now, in the absence of bromine, can be first performed by a bromine-free condition to lead to **4** in the highest yield. Our oxidation provides the best result of trimellitic acid **4** from **1** by a bromine-free catalytic system.

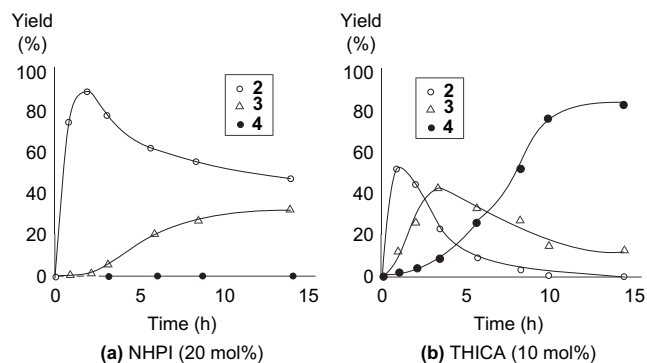
Since it is possible to form three positional isomers of mono and dicarboxylic acids, **2** and **3**, in the oxidation of **1**, it is interesting to clarify which methyl group in **1** is preferentially oxidized.

Thus, we examined the oxidation of **1** under mild conditions at 100 °C for 1 h under atmospheric dioxygen and obtained 2,4-dimethylbenzoic acid (**2a**) (27%), 2,5-dimethylbenzoic acid (**2b**) (11%), and 3,4-dimethylbenzoic acid (**2c**) (26%) as well as dicarboxylic acids consisting of **3a** (2%), **3b** (5%), and **3c** (5%) (Eq. 1). The amounts of these mono and dicarboxylic acids were confirmed as their methyl esters by esterification of the resulting carboxylic acids with diazomethane. From consideration of the electron-donating effect of the methyl groups and their steric effect, it is reasonable that **2a** and **2c** are preferentially formed rather than **2b**. On the other hand, in the oxidation of a 1:1:1 mixture of **2a**, **2b**, and **2c** under the same conditions as Eq. 1, the conversion of **2a**, **2b**, and **2c** was 17%, 32%, and 24%, respectively. These results indicate that **2b** is the most subject to autoxidation among dimethylbenzoic acids.



It is interesting to compare the catalytic performance of THICA with that of NHPI for the oxidation of **1**. Thus, the oxidation of **1** with O<sub>2</sub> (1 atm) by THICA (10 mol %) in the presence of Co(OAc)<sub>2</sub> (2 mol %) and Mn(OAc)<sub>2</sub> (0.5 mol %) at 100 °C was compared with that by NHPI (20 mol %) under these conditions. The time-dependence curves of products, **2**, **3**, and **4** for the oxidation of **1** by NHPI and THICA are shown in Figure 1a and b, respectively.

By the NHPI catalyst, **1** was found to be rapidly oxidized to monocarboxylic acid **2** in over 90% yield within 2 h. However, dicarboxylic acid **3** was rarely formed at the stage of 2 h and then gradually increased up to 35%, while no trimellitic acid **4** was observed throughout the reaction. That there was no oxidation of **3** to **4** is believed to be due to the deactivation by the decomposition of NHPI and/or the adduct formation of the resulting radical species with the phthalimide-*N*-oxyl (PINO) radical because of the slow diffusion of oxygen into the liquid phase from the gaseous phase at the early stage of the reaction.<sup>7</sup> On the other hand, oxidation of **1** to **2** by THICA proceeded more slowly than that by NHPI, since THICA is less active but more

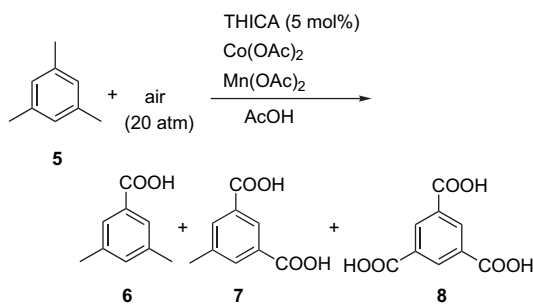


**Figure 1.** Time-dependence curves for the oxidation of **1** by THICA or NHPI; reaction conditions: **1** (1 mmol), THICA (10 mol %) or NHPI (20 mol %),  $\text{Co}(\text{OAc})_2$  (2 mol %),  $\text{Mn}(\text{OAc})_2$  (0.5 mol %),  $\text{AcOH}$  (2.5 mL),  $\text{O}_2$  (1 atm), and 100 °C.

stable than NHPI. As a result, THICA is not decomposed during the reaction and can oxidize **1** to **4**. These results indicate that THICA served as a more efficient catalyst than NHPI for the oxidation of reactive trimethylbenzenes to benzenetricarboxylic acids.

We next tried the aerobic oxidation of 1,3,5-trimethylbenzene (mesitylene) (**5**) under air (20 atm) by THICA in the presence of  $\text{Co}(\text{OAc})_2$  and  $\text{Mn}(\text{OAc})_2$  (Table 2). To our knowledge, there has been no study on the aerobic oxidation of **5** except for several patent works.<sup>8</sup> 1,3,5-Benzenetricarboxylic acid (trimesic acid) (**8**) is known to be used as a cross-linking agent for polymers, plasticizers etc.<sup>9</sup>

**Table 2.** Aerobic oxidation of 1,3,5-trimethylbenzene (**5**) by THICA under selected conditions<sup>a</sup>



Entry	Co(II)/Mn(II) (mol %)	Temp (°C)	Time (h)	Yield (%) <sup>b</sup>		
				6	7	8
1	0.5/0.5	120	6	n.d.	41	48
2	0.5/0.5	150	6	n.d.	9	82
3	2/0.5	120	6	n.d.	6	85
4 <sup>c</sup>	0.5/0.5	120	6	n.d.	25	65

<sup>a</sup> Compound **5** (1 mmol) was oxidized under air (20 atm) in the presence of THICA (5 mol %),  $\text{Co}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ , and  $\text{Mn}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$  in  $\text{AcOH}$  (2.5 mL) at 120 or 150 °C for 6 h.

<sup>b</sup> Conversion was over 99% in each run.

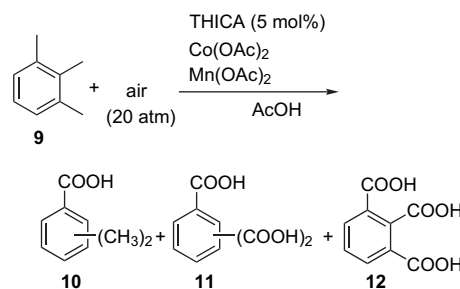
<sup>c</sup>  $\text{ZrO}(\text{OAc})_2$  (0.5 mol %) was added.

The oxidation of **5** by THICA (5 mol %) in the presence of  $\text{Co}(\text{OAc})_2$  (0.5 mol %) and  $\text{Mn}(\text{OAc})_2$  (0.5 mol %) at 120 °C for 6 h afforded dicarboxylic acid (**7**) (41%) and trimesic acid **8** (48%), but 3,5-dimethylbenzoic acid (**6**) was not detected (entry 1). The reaction was carried out at 150 °C

under these conditions giving **8** in 82% yield (entry 2). When the amount of  $\text{Co}(\text{OAc})_2$  was increased to 2 mol %, trimesic acid **8** was obtained in high yield (85%) even at 120 °C (entry 3). It was found that a moderate effect of  $\text{ZrO}(\text{OAc})_2$  was observed in the oxidation of **5** different from that of **1** (entry 4). In patent works on the oxidation of **5**, the best result of **8** is 88% yield when **5** was oxidized by a Co/Mn/Br system under 20 atm of air at 220 °C.<sup>4d</sup> It is important to note that the present oxidation by THICA can be carried out even at 120 °C to give **8** in comparable yield with that by the Co/Mn/Br system, while the oxidation by the Co/Mn/Br system is carried out at higher temperature (220 °C).

The oxidation of 1,2,3-trimethylbenzene (hemimellitene) (**9**) was examined under the same conditions as in Table 2 (Table 3).

**Table 3.** Aerobic oxidation of 1,2,3-trimethylbenzene (**9**) by THICA under selected conditions<sup>a</sup>



Entry	Co(II)/Mn(II) (mol %)	Temp (°C)	Conv. (%)	Yield (%) <sup>b</sup>		
				10	11	12
1	0.5/0.5	120	6	14	16	14
2	2/2	120	6	2	11	40
3 <sup>c</sup>	0.5/0.5	120	6	5	29	41
4	0.5/0.5	150	6	5	21	29
5 <sup>c</sup>	0.5/0.5	150	6	n.d.	5	81

<sup>a</sup> Compound **9** (1 mmol) was oxidized under air (20 atm) in the presence of THICA (5 mol %),  $\text{Co}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$ , and  $\text{Mn}(\text{OAc})_2 \cdot 4\text{H}_2\text{O}$  in  $\text{AcOH}$  (2.5 mL) at 120 or 150 °C for 6 h.

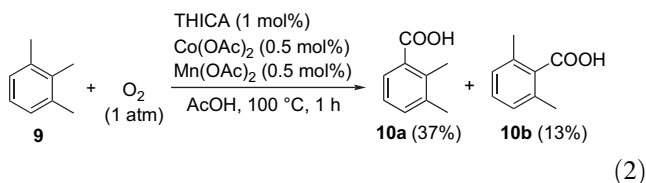
<sup>b</sup> Conversion was over 99% in each run.

<sup>c</sup>  $\text{ZrO}(\text{OAc})_2$  (0.5 mol %) was added.

The oxidation of **9** was difficult to carry out selectively at 120 °C different from that of **1** or **5**, and about a 1:1:1 mixture of mono, di, and tricarboxylic acids, **10**, **11**, and **12**, was obtained in low yields (entry 1). When the amount of  $\text{Co}(\text{OAc})_2$  and  $\text{Mn}(\text{OAc})_2$  was increased to 2 mol %, hemimellitonic acid **12** was obtained in 40% yield. By adding  $\text{ZrO}(\text{OAc})_2$  (0.5 mol %) to the THICA/ $\text{Co}(\text{OAc})_2$ / $\text{Mn}(\text{OAc})_2$  system, the oxidation of **9** at 120 °C for 6 h led to **10** (5%), **11** (29%), and **12** (41%) (entry 3). A similar tendency was observed in the oxidation at 150 °C. When **9** was oxidized at 150 °C, **10**, **11**, and **12** were obtained in 5, 21, and 29% yields, respectively (entry 4). However, in the presence of  $\text{ZrO}(\text{OAc})_2$  (0.5 mol %) under these conditions, the oxidation resulted in **12** in high yield (81%) (entry 5). In the oxidation of **9**, a remarkable addition effect of  $\text{ZrO}(\text{OAc})_2$  was observed. In order to obtain information on the formation of mono and dicarboxylic acids, **9** was oxidized at low temperature (100 °C).

The oxidation of **9** by THICA/ $\text{Co}(\text{OAc})_2$ / $\text{Mn}(\text{OAc})_2$  at 100 °C for 1 h afforded 2,3-dimethylbenzoic acid (**10a**)

(37%) in preference to 2,6-dimethylbenzoic acid (**10b**) (13%) (Eq. 2).



In the oxidation of **9** at 100 °C, no di and tricarboxylic acids were formed. The preferential formation of **10a** over **10b** indicates that the steric effect of the methyl group is a more important factor than the electron-donating effect.

In conclusion, we have carried out the first systematic study on the aerobic oxidation of trimethylbenzenes and developed an efficient halogen-free route to 1,2,4-benzenetricarboxylic acid **4**, which is an important polymer material, using THICA as a key catalyst.

### 3. Experimental

#### 3.1. General procedure

Starting materials and catalysts were purchased from commercial sources and used without further treatment. Yields were estimated from the peak areas based on 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 (OV-17). <sup>1</sup>H and <sup>13</sup>C NMR spectra were measured at 270 and 400 MHz, respectively, in chloroform-*d* with Me<sub>4</sub>Si as the internal standard. Infrared (IR) spectra were measured using NaCl or KBr pellets. GC–MS were obtained at ionization energy of 70 eV. All products were identified by comparison of the isolated products with authentic samples.

#### 3.2. Preparation of *N,N',N''*-trihydroxyisocyanuric acid (THICA)

THICA was prepared by a modified literature procedure.<sup>10</sup> 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 the temperature was raised 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 tribenzoyloxy-1,3,5-triazine-2,4,6-(1*H*,3*H*,5*H*)-trione (TBTA) (5.1 g) in 23% yield.

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. The X-ray analysis of THICA indicates that three OH groups are situated at the same plane.

**TBTA**: <sup>1</sup>H NMR δ 7.52 (m, 2H), 7.42 (m, 3H), 5.1 (s, 2H); <sup>13</sup>C NMR δ 144.83, 133.47, 129.52, 129.04, 128.35, 78.482; IR (KBr) 1740s, 1401s, 1197m, 1001s, 750s, 696s cm<sup>-1</sup>.

**THICA**: <sup>1</sup>H NMR δ 11.03 (s, 3H); <sup>13</sup>C NMR δ 146.65; IR (KBr) 3539s, 3166s, 2827s, 1720s, 1433s, 1211m, 1010s, 701s cm<sup>-1</sup>.

#### 3.3. Procedure for oxidation of substituted toluenes under dioxygen atmosphere

An acetic acid solution (5 mL) of substrate (3 mmol), THICA, Co(OAc)<sub>2</sub> (0.5 mol %) was placed in a 50-mL pear-shaped flask with a balloon filled with O<sub>2</sub>. The mixture was stirred at 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 the isolated products with authentic samples.

#### Acknowledgements

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