Research Paper



# An efficient synthesis of 2,3,5-trimethylbenzoquinone by metal-free oxidation of 1,2,4-trimethylbenzene

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#### Abstract

The oxidation of 1,2,4-trimethylbenzene with phthaloyl peroxide has been investigated under solvent-free and optimized conditions. 2,3,5-Trimethylbenzoquinone was obtained with great purity in 92% yield at 95% conversion of 1,2,4-trimethylbenzene at 120°C for 2.5 h under solvent-free conditions. The important factors such as the efficiency of the different cyclic acid anhydrides or carboxylic acid peroxides, the concentration of phthalic anhydride and 30%  $H_2O_2$ , the reaction time, the effect of solvent system, and the reaction temperature have been studied. An important advantage of this oxidizing system, aside from the organic solvent-free conditions, is that it is non-toxic, eco-friendly, and inexpensive. In addition, this methodology will be of great use in the preparation of commercially valuable benzoquinones from the corresponding aromatic compounds.

### **Keywords**

1,2,4-trimethylbenzene, 2,3,5-trimthylbenzoquinone, metal-free oxidation, phthaloyl peroxide

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# Introduction

The oxidation of aromatic C–H bonds and the synthesis of benzoquinones from aromatic compounds is a central facet of the chemical and pharmaceutical industry.<sup>1–4</sup> The natural products with benzoquinone moiety exhibit an attractive pharmacological profile as antitumor, antimicrobial, and cardiovascular activities.<sup>5–7</sup> In addition, synthetic benzoquinones are important building blocks in the preparation of pharmaceutical ingredients.<sup>8</sup> 2,3,5-Trimethylbenzoquinone (TMBQ) is a commercially valuable compound, and it can be reduced to 2,3,5-trimethylhydroquinone (TMHQ), which is known to be an important starting material for the synthesis of vitamin-E. In the literature, various processes for preparing TMBQ by the oxidation of 2,3,5-trimethylphenol (TMP) or 1,2,4-trimethylbenzene (TMB) have been reported.<sup>9–16</sup> However,

most of the reported methods have not been advantageous from a commercial and large-scale production viewpoint because they require commercially non-available or expensive starting materials and reagents and need large quantities of organic solvents, multi-step synthesis in harsh reaction conditions, or use toxic metal catalysts.<sup>13</sup> Considering these facts, there is still a need to develop a commercially viable,

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Scheme I. Oxidation of I,2,4-trimethylbenzene to

2,3,5-trimethylbenzoquinone using phthaloyl peroxide.

non-infringing, and scalable synthetic methodology for the preparation of TMBQ.

Yuan et al.<sup>17</sup> and Dragan et al.<sup>18</sup> described a metal-free oxidation of aromatic hydrocarbons to corresponding phenols using phthaloyl and malonoyl peroxides, respectively. However, a method for the preparation of TMBQ by straight oxidation of TMB using phthaloyl or malonoyl peroxide has yet to be reported. These observations prompted us to develop a simple, efficient, and commercially viable synthetic method for the preparation of TMBQ from a readily available starting material, that is, TMB using phthaloyl peroxide in a solvent or under solvent-free conditions (Scheme 1).

### **Results and discussion**

We initially examined the efficiency of different cyclic acid anhydride or carboxylic acid peroxides for the oxidation of TMB to TMBQ under solvent-free conditions at 120°C or reflux temperature for 2.5 h. Phthaloyl peroxide (generated in situ by the reaction of 30%  $H_2O_2$  on phthalic anhydride) was found to be the most effective oxidizing agent for the oxidation of TMB in TMBQ among all the carboxylic acid and cyclic anhydride peroxides evaluated (Table 1).

We then examined the effect of various concentrations of phthaloyl peroxide on the oxidation of TMB into TMBQ using different molar concentration ratios between phthalic acid, 30%  $H_2O_2$ , and TMB. Optimization of the reaction conditions led us to determine that the use of 3-mol equivalent of phthalic anhydride and 8-mol equivalent of 30%  $H_2O_2$  against 1-mol equivalent of TMB under solvent-free conditions at 120°C for 2.5 h gave the highest yield of TMBQ produced (Table 2).

The dependence of oxidation efficiency of phthaloyl peroxide on TMB production at various temperatures (60°C–140°C) was investigated. The conversion of TMB to TMBQ increased with the raise in reaction temperature when the optimized reaction conditions were kept unchanged. The rate of TMB-to-TMBQ conversion leveled off at 120°C, and the formation of TMBQ was optimal at the same temperature. A further increase in the reaction





TMB: 1,2,4-trimethylbenzene;TMBQ: 2,3,5-trimethylbenzoquinone. <sup>a</sup>Reaction conditions: I mmol of TMB, 3 mmol of cyclic acid anhydride or carboxylic acid, 8 mmol of 30%  $H_2O_2$ , 120°C, solvent free, 2.5 h. <sup>b</sup>Conversion of TMB to TMBQ. <sup>c</sup>Isolated yield of the TMBO.

temperature caused a decrease in the selectivity of TMBQ because it was further oxidized to form some unknown side products. These results indicated that the reaction temperature is a key factor in the oxidation of TMB to TMBQ (Table 3).

We also investigated the influence of the reaction time on the oxidation of TMB to TMBQ with phthaloyl peroxide. The rate of conversion of TMB to TMBQ reached a maximum (95%) at 2.5 h time point. A further increase of the reaction time induced a slight decrease of the TMBQ content because of over oxidation by excess  $H_2O_2$ , producing other unknown by-products. Therefore, we suggest that 2.5 h is the optimal reaction time at 120°C for an oxidation reaction of TMB into TMBQ. These results indicated that the reaction time played a key role in the oxidation of TMB into TMBQ (Table 4).

Finally, we examined the effect of various solvents on the oxidation of TMB into TMBQ using phthaloyl peroxide (10 volumes of solvent by weight of TMB). The conversion of TMB to TMBQ was found to increase under a solventfree reaction under the previously optimized reaction conditions (Table 5). **Table 2.** Effect of amount of phthalic anhydride and 30% H<sub>2</sub>O<sub>2</sub> on oxidation of TMB to TMBQ.



| Molar ratio |                    |                                   | Conversion | Yield                |
|-------------|--------------------|-----------------------------------|------------|----------------------|
| ТМВ         | Phthalic anhydride | 30% H <sub>2</sub> O <sub>2</sub> | (moi %)ª   | (mol %) <sup>s</sup> |
| 1.0         | 2.0                | 6.0                               | 62         | 58                   |
| 1.0         | 3.0                | 6.0                               | 74         | 70                   |
| 1.0         | 4.0                | 6.0                               | 75         | 72                   |
| 1.0         | 2.0                | 8.0                               | 85         | 81                   |
| 1.0         | 3.0                | 8.0                               | 95         | 92                   |
| 1.0         | 4.0                | 8.0                               | 92         | 90                   |
| 1.0         | 2.0                | 10.0                              | 76         | 72                   |
| 1.0         | 3.0                | 10.0                              | 90         | 87                   |
| 1.0         | 4.0                | 10.0                              | 88         | 86                   |

TMB: I,2,4-trimethylbenzene;TMBQ: 2,3,5-trimethylbenzoquinone. <sup>a</sup>Conversion of TMB to TMBQ.

<sup>b</sup>Isolated yield of TMBQ.

 Table 3. Effect of reaction temperature on oxidation of TMB to TMBQ using phthaloyl peroxide.<sup>a</sup>



TMB: 1,2,4-trimethylbenzene; TMBQ: 2,3,5-trimethylbenzoquinone. <sup>a</sup>Reaction conditions: I mmol of TMB, 3 mmol of phthalic anhydride, 8 mmol of 30%  $H_2O_2$ , solvent free, 2.5 h. <sup>b</sup>Conversion of TMB to TMBQ.

<sup>c</sup>lsolated yield of TMBQ.

In summary, phthaloyl peroxide, which was generated in situ by the oxidation of phthalic anhydride with aqueous hydrogen peroxide  $(30\% H_2O_2)$ , was found to be highly efficient for the selective oxidation of TMB to TMBQ, which was best achieved using a reaction time of 2.5 h, carried out at 120°C, in a solvent-free environment and with a molar ratio of 1:3:8 of TMB, phthalic anhydride, 30% H<sub>2</sub>O<sub>2</sub>, respectively. An important advantage of this oxidizing system, aside from the organic solvent-free conditions, is the non-toxic, eco-friendly, and inexpensive nature of such chemical reaction. In addition, this methodology could be of





clsolated yield of TMBQ.

great use in the preparation of commercially valuable benzoquinones from the corresponding aromatic compounds.

# **Experimental**

All starting materials, reagents, and solvents are commercially available and were used without further purification. Melting points were determined with an X-4 apparatus and are uncorrected. The nuclear magnetic resonance (NMR) spectra were recorded on a Bruker (NY, USA) Ascend 600 spectrometer using tetramethylsilane (TMS) as an internal standard. The reactions were monitored by thin-layer chromatography (TLC; HG/T2354-92, GF254), and compounds were visualized on TLC with ultraviolet (UV) light. The purity of products was determined by high-performance liquid chromatography (HPLC) using a Shimadzu (Tokyo, Japan) LC-20A series instrument.

### Method-1: typical procedure for the oxidation of TMB to TMBQ using phthaloyl peroxide under solvent-free conditions

To a heterogeneous mixture of phthalic anhydride (44.43 g, 0.3 mol) and 30%  $H_2O_2$  aqueous solution (90.69 g; 0.8 mol; *caution*: heat the contents slowly, as reaction is exothermic and peroxides are explosive in nature) heated at 120°C, TMB (12.02 g; 0.1 mol) was added using a dropping funnel for 15–20 min. The reaction mixture was stirred for 2.5 h at 118°C–120°C and then was cooled to room temperature. Ethylacetate (125 mL) was added, stirred for 15 min at room temperature, and then removed the solids by filtration, washed the solids with ethylacetate (2 × 50 mL). Diluted the combined filtrate with H<sub>2</sub>O (50 mL). The two phases were separated, and the aqueous layer was extracted with ethylacetate (50 mL). The combined organic layers were washed with water (100 mL)

| Solvent           | Temperature (°C) | Conversion (mol %) <sup>b</sup> | Yield (mol %) <sup>c</sup> |
|-------------------|------------------|---------------------------------|----------------------------|
| n-Hexane          | Reflux           | 68                              | 66                         |
| <i>n</i> -Heptane | Reflux           | 76                              | 72                         |
| No solvent        | 120              | 95                              | 92                         |
| Ethylacetate      | Reflux           | 88                              | 85                         |
| Water             | Reflux           | 85                              | 81                         |

Table 5. Effect of solvent on oxidation of TMB to TMBQ using phthaloyl peroxide.<sup>a</sup>

TMB: 1,2,4-trimethylbenzene;TMBQ: 2,3,5-trimethylbenzoquinone.

<sup>a</sup>Reaction conditions: I mmol of TMB, 3 mmol of phthalic anhydride, 8 mmol of 30% H<sub>2</sub>O<sub>2</sub>, I.2 mL of solvent or solvent free, 2.5 h. <sup>b</sup>Conversion of TMB to TMBO.

<sup>c</sup>lsolated yield of TMBQ.

and brine (50 mL), dried on anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated to dryness under vacuum. The residue was purified by flash chromatography with a mixture of hexane and ethylacetate (95:5 v/v) to give the title compound as an orange-colored solid (13.81 g), yield: 92%. <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) δ 6.54 (s, 1H), 2.12 – 1.92 (m, 9H). m.p. 29°C; literature reference<sup>11</sup> m.p. 31°C–32°C.

# Method-2: typical procedure for the oxidation of TMB to TMBQ using phthaloyl peroxide in a solvent

To a heterogeneous mixture of phthalic anhydride (44.43 g, 0.3 mol) and 30%  $H_2O_2$  aqueous solution (90.69 g; 0.8 mol) in a solvent (120.2 mL) heated to reflux (caution: heat the contents slowly, as reaction is exothermic and peroxides are explosive in nature), TMB (12.02 g; 0.1 mol, exothermic reaction) was added using dropping a dropping funnel for 15-20 min. The reaction mixture was stirred for 2.5 h at the reflux temperature and then was cooled to room temperature. Ethylacetate (125 mL) was added, stirred for 15 min at room temperature, and then removed the solids by filtration, washed the solids with ethylacetate  $(2 \times 50 \text{ mL})$ . Diluted the combined filtrate with H<sub>2</sub>O (50 mL). The two phases were separated, and the aqueous layer was extracted with ethylacetate (50 mL). The combined organic layers were washed with water (100 mL) and brine (50 mL), dried on anhydrous Na<sub>2</sub>SO<sub>4</sub>, and concentrated to dryness under vacuum. The residue was purified by flash chromatography with a mixture of hexane and ethylacetate (95:5 v/v) to give the title compound as an orange-colored solid (9.91-12.31 g), yield: 66-81%. 1H NMR (300 MHz, CDCl<sub>3</sub>) δ 6.54 (s, 1H), 2.12 - 1.92 (m, 9H). m.p. 29°C; literature reference<sup>11</sup> m.p. 31°C-32°C.

# Safety warning

Peroxides are potentially explosive. You are strongly advised to check on the precautions that should be followed when handling the peroxides mentioned in this paper.

#### **Declaration of conflicting interests**

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