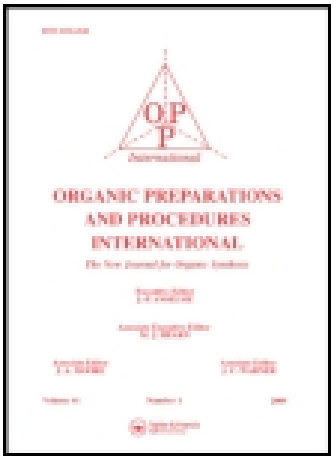

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OPPI BRIEF

An Improved Preparation of 2,6-di-(*t*-Butyl)-4-methylphenol

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As a typical sterically hindered phenolic anti-oxidant, 2,6-di-(*t*-butyl)-4-methylphenol, also known as *butylated hydroxytoluene* (or *BHT*), is widely used in rubber, plastic, paint, jet fuels, petroleum products, bio-diesel, cosmetics, food and pharmaceuticals due to its strong anti-oxidant power, low volatility and sturdiness.[1–3] In addition, BHT has become important for the preparation of other compounds such as 3,5-di-(*t*-butyl)-4-hydroxybenzaldehyde,[4] 3,5-di-(*t*-butyl)-4-hydroxybenzyl bromide[5] and 2,6-di-(*t*-butyl)-1,4-benzoquinone.[6] Recently, BHT has been shown to display anti-tumor[7] and anti-oxidant[8] activities and to be effective in protecting against hepato-toxicity.[9] Thus BHT has also become a lead compound for the development of various drugs and an intermediate for the synthesis of other drugs or drug candidates. With its ever-increasing utility in the food and pharmaceutical industries, it is imperative to understand the nature and toxicity of impurities that might be produced during its manufacture in order to increase the purity of the BHT produced. Herein, we report a study on the reaction of *p*-cresol with isobutylene to prepare BHT.

Over the past few decades, a considerable amount of work has been devoted to the use of novel acid catalysts such as ion exchange resins,[10] phosphorus tungsten heteropoly acid,[11] ionic liquids[12] and $AlCl_3$ supported on Montmorillonite[13] to perform the Friedel-Crafts alkylation of *p*-cresol with isobutylene. Although many of these catalysts do exhibit desirable features such as minimal corrosion of the equipment, high selectivity, and recyclability, their high cost, variable catalytic activity, and long production cycle have limited their utilization on a large scale. In comparison, conc. sulfuric acid,[14,15] has the advantages of high catalytic activity, low cost, and ready availability. Thus, it has been utilized widely in the production of BHT in spite of the fact that it can result in corrosion of the equipment and formation of impurities.

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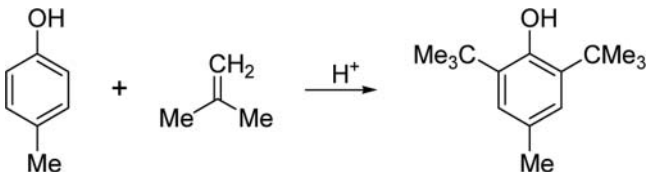
Table.
Preparation of BHT [a)]

Entry	Yield [b)](%)	Thiourea(g)	Ratio [c)] (%)		
			Reaction mixture	Crude BHT	Purified BHT
1	72.3 [d)]	0.0	92.94 / 0.54	93.51 / 0.59	97.23 / 0.45
2	78.8 [e)]	0.0	96.38 / 0.19	98.09 / 0.47	99.51 / 0.28
3	81.1 [e)]	0.8	95.17 / 0.15	99.10 / 0.28	99.75 / 0.16
4	80.9 [e)]	12.0	96.44 / 0.12	98.79 / 0.16	99.85 / 0.11

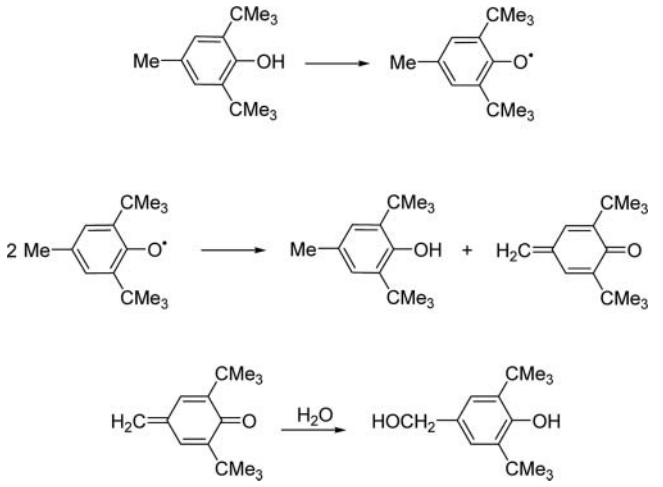
a)Using 80.0 g of *p*-cresol except for *Entry 4* when 1.2 kg was used.
b)Yield of pure BHT.
c)Ratio of BHT to 2,6-di-(*t*-butyl)-4-(hydroxymethyl)phenol.
d)Using 3% by weight of H_2SO_4 as catalyst.
e)Using 6% by weight of anhydrous TsOH as catalyst.

Initially, when 3% of conc. sulfuric acid (by weight) was used as the catalyst, the reaction was complete within 7 h. However, GC monitoring showed that the conversion to BHT was less than 95%, even after neutralization, filtration, washing, and recrystallization, the purity of the purified BHT was less than 98% (*Entry 1, Table*). One of the major impurities (more than 0.4%) generated during the reaction was a species with the retention time of 5.4 min and the percentage of this compound increased significantly during the work-up and subsequent recrystallization could not decrease it to any extent. On the other hand, the contents of other impurities identified as 2-(*t*-butyl)-4-methylphenol and 3,3′,5,5′-tetra(*t*-butyl)silbene-4,4-quinone decreased dramatically upon work-up and recrystallization. Therefore, it was determined that the compound with a retention time of 5.4 min was the major impurity of the manufacturing process and that the key to improving the purity of BHT was to efficiently control and/or eliminate the formation of this compound especially during the work-up.

In order to devise effective means to control the generation of the major impurity, it was necessary to elucidate its structure. Because its concentration in both the reaction mixture and the crude product was less than 1%, it was very difficult to isolate from the crude BHT or even from the mother liquor. It was supposed that the major impurity might be an oxidation product of BHT based on the observation that its quantity increased during the work-up. Treatment of BHT with various oxidizing agents indeed increased the amount of the impurity and when BHT was treated with potassium permanganate in ethanol the amount of the impurity increased to about 20% by GC. However, we still were unable to isolate it from the mixture because the similar polarity of the components made chromatographic separation difficult. On the other hand, possible oxidation products of BHT such as 3,5-di-(*t*-butyl)-4-hydroxybenzaldehyde, 3,5-di-(*t*-butyl)-4-hydroxybenzoic



Scheme 1



Scheme 2

acid, 2,6-di-(*t*-butyl)-benzo-quinone and 3,3',5,5'-*tetra*-(*t*-butyl)stilbene-4,4-quinone[16,17] were synthesized and isolated but their gas chromatographic retention times were different from the 5.4 minute of the impurity. When BHT was oxidized to 3,5-di-(*t*-butyl)-4-hydroxybenzaldehyde using bromine in *t*-butanol, the amount of the major impurity in the filtrate after the oxidation product had been collected, was about 30%. Extraction of the filtrate and chromatography on silica gel with dichloromethane as the eluent gave the pure product as a pale yellow solid established to be 2,6-di-*(t*-butyl)-4-(hydroxymethyl) phenol by ^{1}H NMR, MS, and direct comparison with an authentic sample.[15] To the best of our knowledge, this is the first time that the structure of this impurity in the production of BHT has been elucidated.

BHT can be oxidized to various products under different conditions, but the conversion of BHT to 2,6-di-(*t*-butyl)-4-(hydroxymethyl)phenol during its manufacturing process has not been studied. The process may be viewed to proceed as shown in *Scheme 2*.[1] Disproportionaton of the phenoxy radical generated from BHT would lead to BHT and the quinone methide, which would react very rapidly with water to afford 2,6-di-(*t*-butyl)-4-(hydroxymethyl)phenol, the major impurity of BHT. *Scheme 2* suggests that in order to minimize the generation of the major impurity, BHT should be prevented from dissociating and water should be avoided during the reaction and the work-up.

Because there is about 2% of water in the conc. sulfuric acid, it was inevitable that the water would react with the quinone methide and that the strong acidity and oxidizing property of the acid would promote the generation of phenoxy radical. Thus these considerations suggest that conc. sulfuric acid might not be an ideal catalyst for the synthesis of BHT of high purity. The use of *anhydrous p*-toluenesulfonic acid (TsOH), was then investigated as catalyst. Because it does not have the two drawbacks of conc. sulfuric acid mentioned above, the experimental results were better. As illustrated in the *Table (Entry 2)*, when 6% weight of the TsOH was used, the contents of the impurity in the reactant, in the crude BHT, and in the purified BHT were lower than that when conc. sulfuric acid was used. The purity of the purified BHT was also about 2% higher. However, the percentage of the impurity increased substantially from 0.2% to 0.5% after work-up. This may have been due to the exposure of the hot mixture to air before it was cooled and neutralized and this exposure accelerated the disproportionation of BHT to the phenoxy

radical. Therefore in order to prevent this occurrence, 1% (by weight) of thiourea was added as an anti-oxidant immediately after completion of the reaction and prior to work-up. The mixture was then cooled with stirring and neutralized, the product was collected, washed and recrystallized. As illustrated in the *Table (Entry 3)*, when TsOH and thiourea were applied, the content of the major impurity in the crude and purified BHT were lower than that of *Entries 1 and 2*. Adoption of these measures led to BHT with a purity above 99.7% in an 81.1% overall yield, in particular, the content of major impurity was decreased to 0.16% and the total amount of all the other impurities was less than 0.1%, this will be of great importance when BHT is used in food and pharmaceutical industries.

To evaluate the possibility of the improved process to be scaled up, 1.2 kg of *p*-cresol was fed in a 5L glass jacketed autoclave, the other operations being the same except that the temperature at which isobutylene was introduced was lowered from 62°C to 56°C and the reaction time was extended to 9 h. The purity of final product was a little higher and the content of the major impurity was a little lower than that in *Entry 3* of *Table*.

In conclusion, an improved preparation of BHT which minimizes the formation of 2,6-di-(*t*-butyl)-4-(hydroxymethyl)phenol, the major impurity and increases the purity of BHT has been designed. Our calculations – based on the manufacture of one ton of BHT – indicates that the higher yield of purer BHT obtained using *p*-toluenesufonic acid requires a lesser amount of *p*-cresol thus compensating for the higher cost of the catalyst. Thus our procedure may constitute a valuable alternative in the preparation of pure BHT for the food and pharmaceutical industries. Moreover, when the improved process was scaled up to 1.2 kg in a 5L glass jacketed autoclave, the results were as good as those performed on a laboratory scale.

Experimental Section

Reagents and solvents were purchased from commercial suppliers and used without further purification. Mps were measured in open capillaries and are uncorrected. The purity of product was determined using a Tianmei GC7900 GC chromatograph. ^{1}H NMR spectra were recorded in $CDCl_3$ on a Bruker Avance (Varian Unity Inova) 400 MHz spectrometer with TMS as the internal standard. MS spectra were performed on a Waters Quattro Premier XE triple quadrupole mass spectrometer. Because the butylation of *p*-cresol with isobutylene is a typical liquid-gas reaction process, a custom-made glass reactor with a flat bottom, a cylindrical body, and three necks to accommodate a condenser, a gas inlet tube, and a thermometer respectively, was utilized in the laboratory-scale experiments. The isobutylene was bubbled through a sintered glass plate just above the bottom thus resulting in a good dispersion of isobutylene and a comparatively long contact time for the isobutylene and *p*-cresol. The gas chromatographic conditions utilized to monitor and analyze the reaction were as follows: GC column: TM-1701 capillary column, the inlet temperature: 280°C, the column temperature: 200°C, FID detector temperature: 280°C, nitrogen flow rate: 45mL/min, hydrogen flow rate: 30mL/min, and injection volume: 1μL. The concentration of sample was about 30mg/mL with dichloromethane as the solvent. The retention time of BHT in the gas chromatogram was about 5.7 min and that of the major impurity was about 5.4 min.

Preparation of BHT using conc. Sulfuric Acid as the Catalyst

The three-necked glass reactor fitted with a condenser, a gas inlet tube, and a thermometer was immersed in a water-bath and melted *p*-cresol (80.0g, 0.74 mol) was added followed

by 98% sulfuric acid (2.4g) with magnetic stirring and heating. The reactor was then purged with nitrogen for about 20 min. When the temperature rose to 62°C, isobutylene was bubbled through the mixture *via* a sintered glass plate. The temperature was maintained at 64–66°C by regulating the flow of isobutylene and the temperature of the water-bath throughout the reaction. TLC on silica plates with ethyl acetate/cyclohexane (1/3 by volume) as the developing solvent and GC were used to monitor the reaction. About 7 h later, the flow of isobutylene was stopped and the reactant was cooled down to room temperature. Water (25 mL) was added to the reactant and the mixture was stirred at 80°C, then, 5% sodium carbonate solution was added until the pH reached 7.5. The solid precipitated upon cooling to room temperature was filtrated, washed with water and dried to afford crude BHT. The purified BHT was obtained after two recrystallizations of the crude BHT from 90% ethanol.

Preparation and Isolation of 2,6-di-(t-Butyl)-4-(hydroxymethyl)phenol

BHT (10.0g, 45.4mmol) was dissolved in *t*-butanol (50mL) at 40°C. Bromine (5.0mL, 97.6mmol) was added dropwise over 1h. After the addition, the mixture was stirred for additional 0.5 h at 40°C. The precipitate was collected and dried to give 3,5-di-(*t*-butyl)-4-hydroxy-benzaldehyde (4.6g, 43.2%). Water (30mL) was added to the filtrate and the mixture was extracted with dichloromethane (20mL×2), then the combined organic phases were evaporated under vacuum to give a pale yellow oil which was subjected to flash column chromatography with dichloromethane as the eluent to give a pale yellow solid, mp. 136–137°C (lit.[16] 135–136°C) whose retention time was 5.4 min in the gas chromatogram. ^{1}H NMR (400MHz, $CDCl_3$): δ7.19(s, 2H), δ5.23(s, 1H), δ4.59(s, 2H), δ1.40(s, 18H), MS (ESI): 235(M-1)$^+$.

Improved Preparation of BHT using p-Toluenesulfonic Acid as Catalyst

The three-necked glass reactor fitted with a condenser, a gas inlet tube, and a thermometer was immersed in a water-bath and melted *p*-cresol (80.0g, 0.74 mol) was added followed by *p*-toluenesulfonic acid (4.8g) with magnetic stirring and heating. The reactor was then purged with nitrogen for about 20 min. When the temperature rose to 62°C, isobutylene was bubbled through the reactant *via* a sintered glass plate. The temperature was maintained at 64–66°C by regulating the flow of isobutylene and the temperature of the water-bath throughout the reaction. TLC (silica gel 1:3 ethyl acetate-cyclohexane) and GC were used to monitor the reaction. About 7h later, the flow of isobutylene was stopped and thiourea (0.8g) was added immediately to the hot mixture which was then cooled while stirring. Water (25mL) was added to the reactant and the mixture was stirred at 80°C. 5% solution of sodium hydroxide was added dropwise to adjust the pH of the solution to about 7.5. After cooling to room temperature, the white solid precipitated was collected, washed with water, and dried to give the crude BHT. The crude BHT was recrystallized from 90% ethanol twice to give the purified BHT, mp 69.9–70.6°C (heavy metals content $< 0.001\%$).

Scale-up Preparation of BHT in a Jacketed Autoclave

The improved procedure for the preparation of BHT was scaled up in a 5L jacketed glass autoclave and 1.2 kg of *p*–cresol was fed for each batch, the operations were the same as above except that the temperature at which isobutylene was introduced was lowered from

62°C to 56°C and the reaction time was extended to 9h. The yield and purity of BHT (*Table, Entry 4*) were very close to those of the experiment performed in the three-necked glass reactor.

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