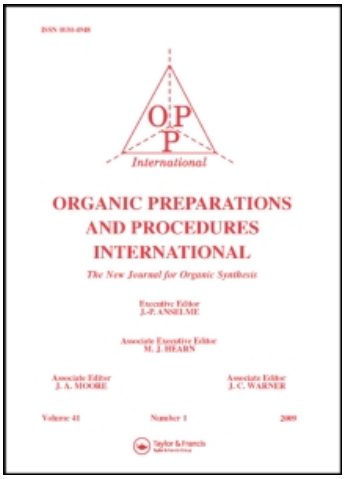

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THE USE OF PIVALOYL CHLORIDE IN THE SELECTIVE SYNTHESIS OF 3-(t-BUTYL)-4-METHOXYPHENOL - A BHA ISOMER

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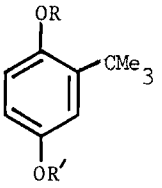
Butylated hydroxyanisole (BHA) has been widely used as an antioxidant to stabilize fatty foods since 1947.[1] Recently, BHA has been found to protect laboratory animals from chemically induced tumorigenesis under various experimental conditions.[2] While the detailed mechanism of protection is still under investigation, *in vitro* observations using benzo[a]pyrene (BP) as a model carcinogen indicate that BHA decreases the formation of active BP metabolites as well as the level of BP-DNA binding.[3] Commercially available BHA contains two isomers in approximately 85:15 ratio of I and II. Reported synthesis of BHA, either by t-



I, R = H, R' = CH_3 IV, R = H, R' = Me_3CCO

II, R = CH_3 R' = H V, R = CH_3, R' = Me_3CCO

III, R = H, R' = H

butylation of hydroxyanisole,[4] or by methylation of t-butylhydroquinone,[5] resulted in a mixture of I and II in approximately the same proportion. Isomer I can be obtained in 99.5% purity from fractional crystallization of the commercial mixture from acetone. Attempts to isolate II from the commercial mixture in large quantity, however, have been complicated by its rapid autoxidation in solution. Pivaloyl chloride has been used

successfully in the synthesis of peptides as a carboxyl protecting group.[6] We like to report the use of this reagent as a phenol protecting group in the synthesis of isomer II without the contamination of isomer I.

Compound III was esterified with pivaloyl chloride in pyridine at 10° to give the monoester IV in excellent yield. The use of pivaloyl chloride served to optimize the steric interactions between the two t-butyl groups. The result was exclusive esterification at the less hindered hydroxyl group of III. Dimethyl sulfate methylation of IV in acetone in the presence of potassium carbonate gave V in quantitative yield. Isomer II was obtained by KOH saponification of V. The overall yield of the synthesis of II was 70% from III.

EXPERIMENTAL

Melting points were taken with a Fisher-Johns melting point apparatus and are uncorrected. IR spectra were recorded on a Beckman Acculab 5 spectrometer. UV spectra were recorded on a Beckman Model 25 spectrophotometer. NMR were obtained on a Varian T60 spectrometer with tetramethyl silane as internal standard. TLC was done on Silica Gel GF plates (Analtech) and was sprayed with 1:1 mixture of 0.1M $FeCl_3$ and 0.1M $K_3Fe(CN)_6$ solutions. Elemental analyses were done by M-H-W Laboratories, Garden City, Michigan.

3-t-Butyl-4-hydroxyphenol trimethyl acetate (III). - To a cooled (5-10°) solution containing 300g (1.8 mol) of t-butylhydroquinone in 1.87 l of pyridine was added 200g (1.66 mol) of prechilled pivaloyl chloride in four equal portions. The reaction mixture was stored at 5-10° for 4 days. The progress of the esterification was checked by TLC. Ten gram portions of pivaloyl chloride, up to 2.0 mol, was added daily until the t-butylhydroquinone was completely reacted. The pyridinium hydrochloride was removed by filtration and the pyridine evaporated in vacuo. The crude product was dissolved in ether. The ether solution was extracted with 6N HCl, washed with water, 10% sodium bicarbonate, and was dried over anhydrous magnesium sulfate. The ether solution was filtered and the

solvent removed in vacuo. The crude product was crystallized from methanol to give 378g (84%) of colorless crystals, mp. 157-159°. IR (CCl_4) 3600 (free OH) and 3460 cm^{-1} (bonded OH), 1750 (ester C=O) and 1727 cm^{-1} (H bonded C=O); UV max (95% EtOH) 201.8 nm (ε 19.4), 228.4 (5.48), 279 (2.59); NMR ($CDCl_3$) δ 1.37 (s, 18), 5.67 (s, 1), 6.33-6.97 (m, 3); mass spectrum (70 eV) m/e (rel. intensity) 250 (27), 166 (100), 151 (61), 123 (5), 57 (48).

Anal. Calcd for $C_{15}H_{22}O_3$: C, 71.97; H 8.86. Found: C, 71.87; H, 9.13.

3-t-Butyl-4-methoxyphenol trimethyl acetate (IV). - To a refluxing suspension of 276g (2 mol) of powdered potassium carbonate and 250g (1 mol) of III in 3 l of dry acetone was added dropwise 150ml (1.5 mol) of dimethyl sulfate over a period of 3.5 hrs. At the end of 24 hrs, the reaction was cooled and the acetone solution collected by decantation. The solid was washed with acetone. The acetone solutions were combined and the solvent removed in vacuo to give 251g (95%) of IV. Recrystallization from methanol yielded white crystalline IV, mp. 67-68°. IR (CCl_4) 1750 cm^{-1} (ester C=O); UV max (95% EtOH) 202.2 nm (ε 18.7); 229.8 (6.88), 278 (2.48); NMR ($CDCl_3$) δ 1.38 (s, 18), 3.82 (s, 3), 6.77-6.93 (m, 3); mass spectrum (70 eV) m/e (rel. intensity) 264 (66), 180 (100), 165 (70), 57 (36).

Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.70; H, 9.40.

3-t-Butyl-4-methoxyphenol (II). - A solution containing 191g (0.72 mol) of IV, 510g (9.1 mol) of potassium hydroxide in 2 l of 50% aqueous EtOH was heated under reflux for 64 hrs under nitrogen atmosphere. The reaction was cooled and was acidified with conc. HCl. The yellowish organic layer was collected. The aqueous layer was extracted with ether (3 X 500ml). The organic layer and extracts were combined, washed with water, saturated sodium bicarbonate solution, and was dried over anhydrous

magnesium sulfate. The ether solution was filtered and the solvent was removed in vacuo. Recrystallization from cyclohexane yielded 114.1g (87.5%) of II, mp. 63.5-64°, lit[4] 62.5°.

NMR[7] ($CDCl_3$) δ 1.31 (s, 9), 3.73 (s,3), 5.45 (s, 1), 6.57-6.83 (m, 3).

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