Preparation of 4-Bromo- and 4-Chloro-3-*t*-butylphenol

Gouki FUKATA, Yukihiro KUBOTA, Shuntaro MATAKA,† Thies THIEMANN,† and Masashi TASHIRO*,†
Department of Food Science and Technology, Faculty of Engineering, Toa University,
2-1, Ichinomiyagakuen-cho, Shimonoseki, Yamaguchi 751
† Research Institute of Advanced Material Study, and Department of Molecular Science and Technology,
Graduate School of Engineering Sciences, Kyushu University, 6-1, Kasuga-kohen, Kasuga, Fukuoka 816
(Received September 20, 1993)

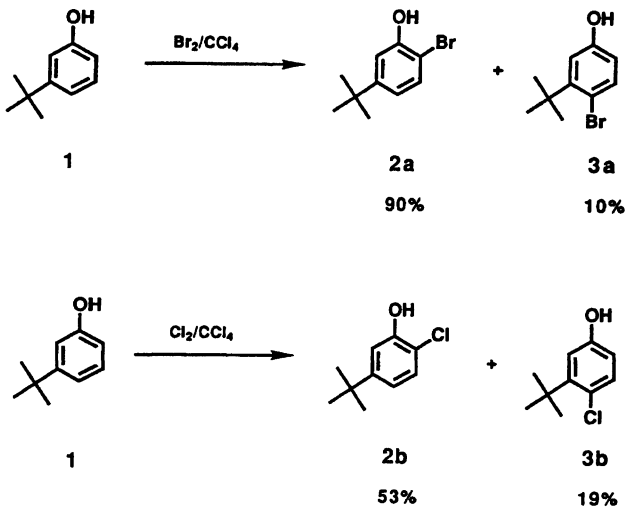
Synopsis. 4-Bromo- and 4-Chloro-3-*t*-butylphenol, two potent fungistatics, were prepared in an efficient 3-step synthesis from commercially available materials. Crucial to the synthesis is the use of halo-substituents as positional protective groups.

We have recently found[1] that 3-*t*-butyl-4-bromo- (**3a**) and 3-*t*-butyl-4-chloro-phenol (**3b**) exhibit a powerful fungistatic activity towards *Aspergillus niger*. Here, we want to report on an efficient synthetic route for both phenols **3a** and **3b**.

A direct halogenation of *m*-*t*-butylphenol (**1**) gives **3a** and **3b** in very low yield, the main products being the *ortho*-halogenated phenols, **2a** and **2b**, as is shown in Scheme 1.

We have, however, reported that the dehalogenation of halophenols under reductive conditions proceeds selectively, depending on the position and type of the halogen. Thus, an *ortho*-bromo substituent can be reduced with zinc powder in a refluxing 10% HCl–EtOH solution (method A), while a *meta*-bromo group can be reduced selectively with zinc-powder in a 10% NaOH solution at room temperature (method B).[2] It is thus possible in some cases to use bromo- (and iodo-) substituents as positional protective groups.[3,4] It has also been found, that in all cases the chloro group was not reduced under the conditions used.

This paper presents an extension of the method described above, whereby bromo and iodo groups are used as positional protective groups in the synthesis of **3a** and **3b** in 3 steps from commericially available **1**.



Scheme 1.

Results and Discussion

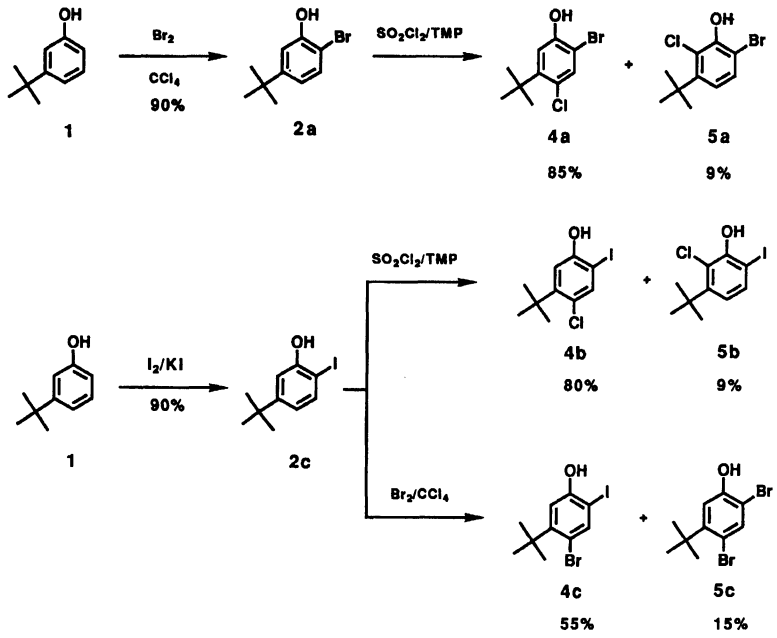
As is shown in Scheme 2, the bromination and iodination of **1** afforded the corresponding 2-bromo- (**2a**)[5] and 2-iodo-5-*t*-butylphenol (**2c**) in high yields. When **2a** and **2c** were treated with SO_2Cl_2 in trimethyl phosphate (TMP), the expected 2-bromo-4-chloro-5-*t*-butylphenol (**4a**) and 4-chloro-2-iodo-5-*t*-butylphenol (**4b**) were obtained in 85 and 80% yield, respectively, together with small amounts (in almost 10% yield) of 6-bromo-2-chloro-3-*t*-butyl- (**5a**)[5] and 2-chloro-6-iodo-3-*t*-butylphenol (**5b**).[5] When CCl_4 was used as a solvent in place of TMP in these chlorinations, the reactions did not proceed quite as facilely to afford the chlorinated compounds. Bromination of **2c** with bromine in CCl_4 afforded the corresponding 4-bromo-2-iodo-5-*t*-butylphenol (**4c**) in 55% yield, together with 2,4-dibromo-5-*t*-butylphenol (**5c**) and **2a** (trace).

The formation of **5c** and **2a** in the bromination of **2c** may be explained by the following pathway, shown in Scheme 3. Compound **2a** is considered to be an intermediate in the formation of **5c**.

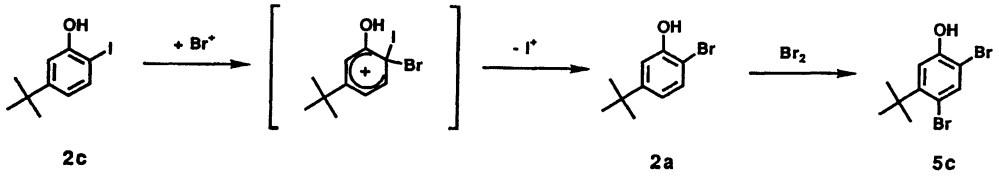
Treatment of **4a** with Zn-powder in a refluxing ethanolic solution (method A) in the presence of 10% HCl for 5 h afforded the desired product **3b** in only poor yield (Scheme 4). However, the reduction of **4b** under the same conditions gave product **3b** in an almost quantitative yield. On the other hand, when **4a** was treated with Zn-powder in a 10% NaOH solution (method B) at 100 °C for 4 h, **3b** was obtained in almost quantitative yield. It was also found that **3b** was smoothly formed in the reduction of **4b** under milder conditions than those for **4a**.

It should also be noted that when Devarda's alloy[6] (Cu–Al–Zn alloy) was used in the reduction of **4a** (method C) at 20 °C for 1 h, **3b** could be isolated in a yield of 90%. It was found that the separation of **4c** from the reaction mixture of **4c**, **5c**, and **2a** was difficult. Thus, it was best to carry out the reduction on the reaction mixture according to method A to give **3a** in a total yield of 60%.

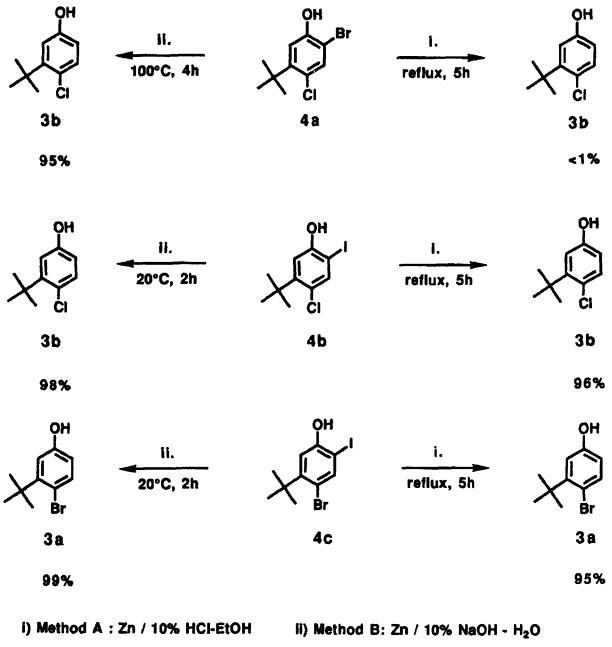
The results mentioned above indicate that the present procedure for the synthesis of **3a** and **3b** is quite effective. Furthermore, it is of interest to note that the *ortho*-deiodination is accelerated by halogen-substituents in the *meta*-position (that is the position *para* to the phenolic group):



Scheme 2.



Scheme 3.



Scheme 4.

4b – **4c** >> **2c**; order of deiodination

The structures of the products were confirmed by their spectral data as well as elemental analyses.

Experimental

All of the melting points are uncorrected. The IR spectra were measured as KBr pellets or as liquid films on a Nippon Bunko (JASCO) IR-A spectrophotometer, and the ^{1}H NMR spectra were determined at 90 MHz with a Hitachi R-900 NMR spectrometer with Me_4Si used as an internal reference. The mass spectra were obtained on a Hitachi M-80 mass spectrometer at 70 eV by using a direct inlet system.

Analytical Procedure: The analyses were carried out by gas chromatography (GC) using a Hitachi 663-50 gas chromatograph; column 5% SE 30, 100 cm: column temperature 200 °C: carrier gas, nitrogen, 20 ml min^{-1}. From the areas of the individual peaks, mol% figures were calculated for each product by the calibration curve method.

5-*t*-Butyl-2-iodophenol (2c): To a stirred solution of *m*-*t*-butylphenol (**1**) (75 g, 0.5 mol) in 10% aq NaOH (250 ml) was added dropwise at room temperature (15 °C) a solution of I_2 (139 g, 0.55 mol)–KI (137 g, 0.83 mol) in water (150 ml). When a milky precipitate deposited in the solution, 450 ml of water was added to the reaction mixture; thereafter, the addition of the I_2–KI solution was continued. After the addition was completed, the solution was stirred for 1.5 h, then acidified with 10% HCl and extracted with benzene (3×250 ml). The benzene extract was washed with a saturated $Na_2S_2O_3$ solution, followed by water, dried over $MgSO_4$ and evaporated in vacuo to afford **2c** (130 g, 94%) as white crystals, mp 45—49 °C, which was purified by recrystallization from aqueous MeOH to afford colorless needles,

mp 48—50 °C; IR (KBr) ν_{OH} 3330 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.28 (9H, s, Bu^t), 5.23 (1H, s, OH, H/D exchange with D_2O), 6.70 (1H, dd, J=3.0 and 9.0 Hz, aromatic H),7.00 (1H, d, J=3.0 Hz, aromatic H), 7.53 (1H, d, J=9.0 Hz, aromatic H); Mass m/z 276 (M^+) (Found: C, 43.45; H, 4.80%. Calcd for $C_{10}H_{31}OI$: C, 43.50; H, 4.75%).

2-Bromo-5-*t*-butyl-4-chlorophenol (4a): A solution of **2a**[5] (2.29 g, 1×10^{-2} mol) in TMP (5 ml) was externally cooled (ice–water bath) to 0 °C. To this cooled, stirred solution was added dropwise and within one min a solution of SO_2Cl_2 (0.82 ml, 1.01×10^{-2} mol) in TMP (5 ml). After the addition was completed, the solution was stirred for another 0.5 h and 0 °C. The reaction was quenched with ice-cold water (50 ml) with the products depositing as a viscous oil. The mixture was extracted with hexane (3×50 ml); the extracts were then combined, dried over $MgSO_4$ and evaporated in vacuo to afford a pale-yellow viscous oil (2.8 g), which was purified by column chromatography on silica gel (Wakogel C-300) using $CHCl_3$ as the eluent. First 6-bromo-3-*t*-butyl-2-chlorophenol (**5a**) (0.24 g, 9.1%) and then compound **4a** (2.44 g, 85.0%) were thereby obtained. Compound **5a** was compared with an authentic sample,[5] mp 65.0—66.5 °C, colorless prisms (hexane).

4a: colorless prisms, mp 35.0—36.5 °C; IR (KBr) ν_{OH} 3510 cm^{-1}; ^1H NMR ($CDCl_3$) δ=1.47 (9H, s, Bu^t), 5.36 (1H, s, OH, H/D exchange with D_2O), 7.10 (1H, s, aromatic H), 7.43 (1H, s, aromatic H); Mass m/z 262, 264, 266 (M^+).

5-*t*-Butyl-4-chloro-2-iodophenol (4b): A solution of **2c** (2.76 g, 1×10^{-2} mol) in TMP (5 ml) and a solution of SO_2Cl_2 (0.82 ml, 1.01×10^{-2} mol) in TMP (5 ml) were treated and worked up as described above, affording a pale-yellow viscous oil (3.1 g), which gave 3-*t*-butyl-2-chloro-6-iodophenol (**5b**) (0.28 g, 9.0%) and compound **4b** (2.47 g, 79.7%). Compound **5b** was compared with an authentic sample,[5] mp 70—72 °C, colorless prisms (pentane).

4b: Colorless needles, mp 48.5—50.0 °C, IR (KBr) ν_{OH} 3400 cm^{-1}, ^1H NMR ($CDCl_3$) δ=1.43 (9H, s, Bu^t), 5.16 (1H, s, OH, H/D exchange with D_2O), 7.06 (1H, s, aromatic H), 7.60 (1H, s, aromatic H); Mass m/z 312 (M^+), 310.

4-Bromo-5-*t*-butyl-2-iodophenol (4c): To a stirred solution of **2c** (2.76 g, 1×10^{-2} mol) in CCl_4 (24 ml) was added dropwise at room temperature (20 °C) within 5 min a solution of Br_2 (0.6 ml, 1.17×10^{-2} mol) in CCl_4 (6 ml). After the solution was stirred for 1 h, additional CCl_4 (50 ml) was added to the solution and the reaction was quenched with an aqueous solution of $Na_2S_2O_3$. The CCl_4 phase was dried over $MgSO_4$ and evaporated in vacuo to afford a pale-brown viscous oil (3.15 g), which was purified by column chromatography on silica gel, using hexane/benzene 1 : 4 as eluent. 2,4-Dibromo-5-*t*-butylphenol (**5c**) (0.46 g, mp 50—63 °C, 15%) and **4c** (1.95 g, 55%) were obtained. Compound **5c** was compared with an authentic sample,[5] mp 62—63 °C, colorless prisms (pentane).

4c: Colorless needles, mp 75.5—76.0 °C, IR (KBr) ν_{OH} 3350 cm^{-1}; ^1H NMR ($CDCl_3$). δ=1.48 (9H, s, Bu^t), 5.18 (1H, s, H/D exchanged with D_2O), 7.08 (1H, s, aromatic H), 7.82 (1H, s, aromatic H); Mass. m/z 356 (M^+), 354.

Compounds **4a**—**4c** were crystalized from a mixture of MeOH and H_2O; their elemental analyses agreed well with the calculated values in C +/− 0.3%, H +/− 0.25%.

Reduction of Halo-*t*-butylphenols: Method A (Using Zn–10% HCl–EtOH): To a mixture of **4c** (3.55 g, 1×10^{-2} mol), zinc powder (7.0 g) and EtOH (200 ml) was added 10% HCl (35 ml). After the mixture was refluxed for 5 h, insoluble material was removed by filtration, while the solution was kept hot. The filtrate was evaporated in vacuo, leaving a pale-brwon viscous oil (2.25 g), which was analyzed by GC. The oil was purified by column chromatography on silica gel, using benzene as eluent to afford **3a** (2.18 g, 95.2%, mp 45—50 °C). Recrystallization from MeOH–H_2O gave pure **3a** as pale-yellow needles, mp 48—50 °C, which was found to be identical with an authentic sample.[1]

Method B (Using Zn–10% NaOH): To a solution of **4a** (2.63 g, 1×10^{-2} mol) in 10% NaOH (100 ml) was added zinc powder (6 g) at room temperature (20 °C). The stirred mixture was heated at 100 °C (bath temp) for 4 h. After the solution was cooled down to room temperature, an insoluble material was filtered off. The filtrate was acidified with 10% HCl and extracted with hexane. The hexane extract was dried over $MgSO_4$ and evaporated in vacuo to afford a pale-yellow viscous oil (1.89 g), which was analyzed by GC. The oil was column chromatographed on silica gel, using benzene as eluent to afford **3b** (1.75 g, 94.7%), which was found to be identical with an authentic sample.[1]

Method C (Using Devarda's alloy–10% NaOH): To a solution of **4a** (2.63 g, 1×10^{-2} mol) in 10% NaOH (100 ml) was added Devarda's alloy (2.6 g) at room temperature (20 °C). The mixture was stirred for 1 h at room temperature, and then worked up as described in method B to afford a pale-yellow viscuous oil (1.75 g), which was analyzed by GC. Pure **3b** was obtained by column chromatography as a colorless viscous oil (1.66 g, 90%).

Preparation of 3a from 1 in 3 Steps: Iodination of **1** (3.0 g, 2×10^{-2} mol) in 10% NaOH (10 ml) with I_2 (5.6 g, 2.2×10^{-2} mol) and KI (5.5 g, 3.3×10^{-2} mol) in water (6 ml) was carried out and worked up as described above to afford crude **2c** (5.3 g). To a solution of **2c** (without further purification) in CCl_4 (48 ml) was added a solution of Br_2 (1.2 ml, 2.34×10^{-2} mol). The bromination was carried out and worked up as described above, affording 6.0 g of a product mixture as a yellow viscuous oil, of which the molar ratio of the products **4c**, **5c**, and **2a** was analyzed by GC to be 70, 26, and 4%. The oil (without further purification) was dissolved in EtOH (360 ml) and treated with 10% HCl (60 ml) and zinc powder (12 g). The mixture was worked up according to method A to afford a viscous oil (4.5 g), which, upon chromatography on silica gel using benzene as eluent, afforded first a mixture of **5c** and **2a** (1.0 g) and then **3a** (2.8 g, 61.1%, based on **1**).

References

1) G. Fukata, Y. Miyoshi, Y. Tsuda, S. Iwata, H. Tsuzuki, and M. Tashiro, *J. Food Hyg. Soc. Jpn.*, **31**, 323 (1990).

2) M. Tashiro and G. Fukata, *J. Org. Chem.*, **42**, 835 (1977).

3) M. Tashiro, H. Watanabe, and O. Tsuge, *Org. Prep. Proced. Int.*, **7**, 43 (1975).

4) M. Tashiro and G. Fukata, *Org. Prep. Proced. Int.*, **8**, 51 (1976).

5) W. W. Kaeding, *J. Org. Chem.*, **26**, 4851 (1961).

6) Commercially available Devarda's alloy was used (Wako Pure Chemicals Industries).