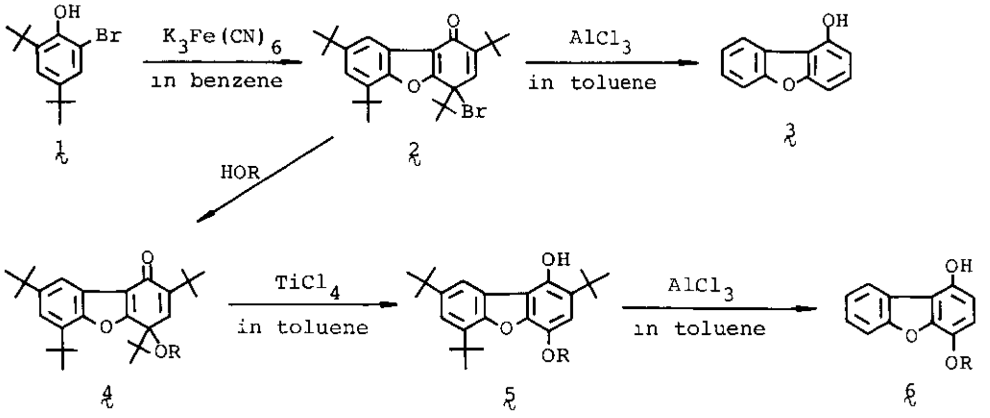
OXIDATIVE COUPLING REACTION OF 2-HALOPHENOLS WITH $K_3Fe(CN)_6$ IN BENZENE SOLUTION

Masashi Tashiro* and Haruo Yoshiya
Research Institute of Industrial Science, and Department of Molecular Science and Technology, Graduate School of Engineering Sciences,
Kyushu University 86, Sakamoto, Kasuga, Kasuga-shi, Fukuoka 816, Japan

Abstract —— The oxidative coupling of twelve 2-halophenols (**1a**-**1ℓ**) was carried out with $K_3Fe(CN)_6$ in benzene solution to obtain the corresponding dibenzofuran derivatives. However, only a small amount of the desired dibenzofurans such as 2,6-di-tert-butyl-8-methoxydibenzofuran-1,4-quinone (**9**) and 4,8-di-tert-butyl-2,6-di-isopropyl-1-hydroxydibenzofuran (**11**) were obtained from 2-bromo-6-tert-butyl-4-methoxy- (**1d**) and 2-bromo-4-tert-butyl-6-isopropylphenol (**1g**), respectively. In the other cases, alternative type of products or tarry materials were formed.

It has been previously reported that the oxidative coupling of 2-bromo-4,6-di-tert-butylphenol (**1**) with $K_3Fe(CN)_6$ in benzene solution afforded the 1-oxodibenzofuran derivative **2**, which was easily converted to several dibenzofuran derivatives (Scheme 1).[1]



Scheme 1

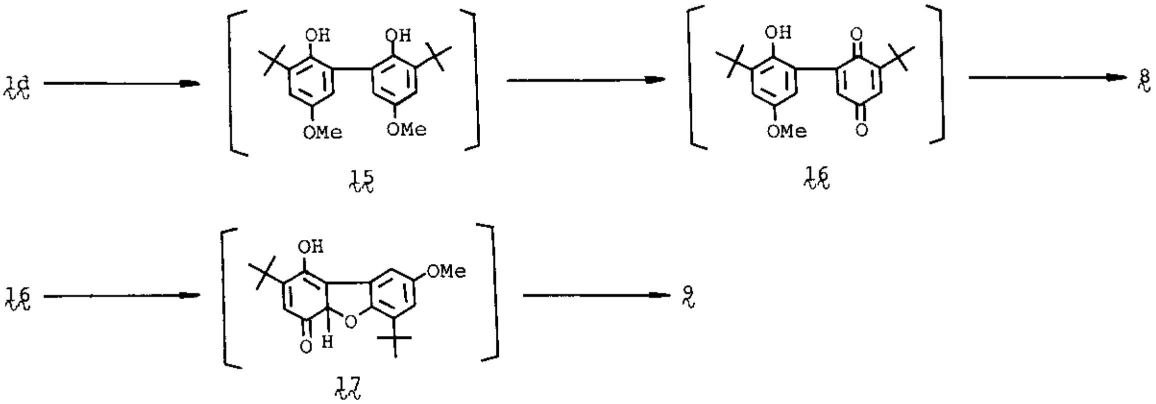
In the present work, the oxidative coupling of some halophenols was investigated to extend the preparative route of dibenzofurans from the corresponding halophenols.

RESULTS AND DISCUSSION

The oxidation of 2-halophenols (**1a**-**1ℓ**) with $K_3Fe(CN)_6$ in benzene solution was carried out at 25°C for 20 min, and the results are summarized in Table 1.

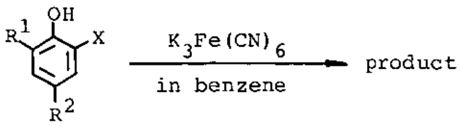
The data in the table show that the types of products depend upon the structures of the phenols. In the cases of **1a**, **1b**, **1e**, **1f**, **1k**, and **1ℓ**, only mixtures of inseparable products and tarry materials were formed.

The isopropyl group of **1c** was selectively oxidized to afford the olefinic derivative **7** in 34% yield. On the other hand, the oxidation of **1d** gave **8** and **9** in 37% and 17% yields. Formation of **8** and **9** suggests that C-C coupling reaction occurred to yield intermediates **15**, **16** and **17**, which were further oxidized to afford the products.



Scheme 2

The case of **1g** afforded C-O coupling compound **10** and the desired dibenzofuran derivative **11** even in low yields. The C-O coupling products **12** and **14** were also obtained from **1h** and **1j**, respectively. The oxidation of **1i** afforded 2-chloro-4-formyl-6-tert-butylphenol (**13**) in very poor yield together with a large amount of a tarry material. As described above, an attempt to find general preparative method of dibenzofurans from 2-halophenols by oxidative coupling was failed. This means that two tert-butyl groups at the positions 4 and 6 of 2-bromophenols are necessary to obtain dibenzofuran derivatives in good yields.



1

X=Br

a: R^1=t-Bu, R^2=Me
b: R^1=t-Bu, R^2=Et
c: R^1=t-Bu, R^2=i-Pr
d: R^1=t-Bu, R^2=OMe
e: R^1=Me, R^2=t-Bu
f: R^1=Et, R^2=t-Bu
g: R^1=i-Pr, R^2=t-Bu
h: R^1=OMe, R^2=t-Bu

X=Cl

i: R^1=t-Bu, R^2=Me
j: R^1=Me, R^2=t-Bu

X=I

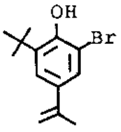
k: R^1=t-Bu, R^2=Me
l: R^1=Me, R^2=t-Bu

Table 1. The oxidative coupling of 2-halophenols (1a-1l) with $K_3Fe(CN)_6$ in benzene solution.[a]

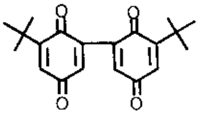
Run	Phenol	Product (%)[b]	Run	Phenol	Product (%)[b]
1	1a	A[c]	7	1g	10 (9), 11 (7)
2	1b	A	8	1h	12 (15)
3	1c	7 (34)	9	1i	13 (4)
4	1d	8 (37), 9 (17)	10	1j	14 (26)
5	1e	A	11	1k	A
6	1f	A	12	1l	A

a) Reaction temperature, 25°C; Time, 20 min. b) Isolated yields are shown.

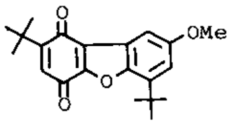
c) A mixture of inseparable products was obtained together with a large amount of tar.



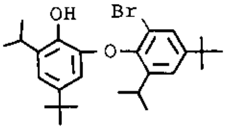
7



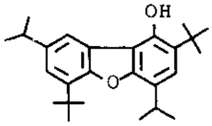
8



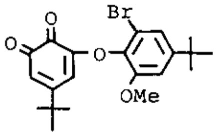
9



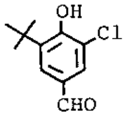
10



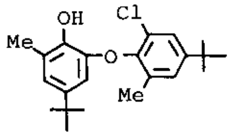
11



12



13



14

EXPERIMENTAL SECTION

All melting points are uncorrected. IR spectra were measured with a Nippon Bunko IR-A spectrometer in KBr pellets or films. ^{1}H-NMR spectra were determined with a Nihon Denshi JEOL FT-100 spectrometer with Me_4Si as an internal standard. Mass spectra were determined by using a Nihon Denshi JMS-01SA-2 mass spectrometer at 75 eV with a direct inlet.

Preparation of 2-Halophenols (**1**)

The 2-halophenols (**1**) used in the present work were obtained by halogenation of corresponding 2,4-disubstituted phenols, which were prepared by the reported methods.

2-t-Butyl-4-methylphenol: pale yellow powder; mp 44.5 ~ 46.5°C, bp 105 ~ 106°C (7 mm); lit.2) bp 126°C (20 mm).

2-t-Butyl-4-ethylphenol: pale yellow oil; bp 103°C (2.5 mm); lit.2) 137°C (20 mm).

2-t-Butyl-4-isopropylphenol: This compound was prepared according to Bowman's procedure.2) Pale yellow oil; bp 103°C (2 mm); IR (NaCl): ν_{OH} 3630 cm^{-1}; NMR ($CDCl_3$): δ 1.22 (6H, d, J = 7 Hz), 1.39 (9H, s), 2.82 (1H, h, J = 7 Hz), 4.65 (1H, br), 6.53 (1H, d, J = 9 Hz), 6.88 (1H, dd, J = 9 Hz, 2 Hz), 7.07 (1H, d, J = 2 Hz); Mass *m/e*: 192 (M^+). Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.53; H, 10.31.

2-t-Butyl-4-methoxyphenol: colorless powder; mp 60 ~ 61°C, bp 134 ~ 135°C (4 mm); lit.3) mp 62 ~ 63°C.

4-t-Butyl-2-methylphenol: colorless oil; bp 97.5 ~ 98.5°C (3 mm); lit.4) 235 ~ 237°C (740 mm).

4-t-Butyl-2-ethylphenol: pale yellow oil; bp 103 ~ 104°C (2 mm); lit.2) 141°C (20 mm).

4-t-Butyl-2-isopropylphenol: This compound was prepared according to Chichibabin's procedure.5) Pale yellow oil; bp 144 ~ 145°C (24 mm); IR (NaCl): ν_{OH} 3420 cm^{-1}; NMR ($CDCl_3$): δ 1.27 (6H, d, J = 8 Hz), 1.28 (9H, s), 3.17 (1H, h, J = 8 Hz), 4.61 (1H, s), 6.62 (1H, d, J = 9 Hz), 7.05 (1H, dd, J = 9 Hz, 2.5 Hz), 7.17 (1H, d, J = 2.5 Hz); Mass *m/e*: 192 (M^+). Anal. Calcd for $C_{13}H_{20}O$: C, 81.20; H, 10.48. Found: C, 81.51; H, 10.23.

4-t-Butyl-2-methoxyphenol: colorless powder; mp 48 ~ 49°C, bp 145 ~ 146°C (30 mm); lit.6) mp 50 ~ 51°C, bp 123 ~ 125°C (12 mm).

Bromination of 2-t-Butyl-4-methylphenol

Typical Procedure

To a solution of 2-t-butyl-4-methylphenol (3.29 g, 20 mmol) in carbon tetrachloride (30 ml) was added slowly bromine (3.4 g, 21 mmol). After the reaction mixture was stirred for 30 min at room temperature, it was poured into aq. $Na_2S_2O_3$ solution and was extracted with ether. The ether extract was washed with water, dried over Na_2SO_4, and evaporated *in vacuo* to leave a residue. The residue was distilled under reduced pressure to afford 3.2 g (66%) of **1a**: bp 113 ~ 114°C (5 mm); IR (NaCl): ν_{OH} 3480 cm^{-1}; NMR ($CDCl_3$): δ 1.38 (9H, s), 2.24 (3H, s), 5.58 (1H, s), 6.96 (1H, d, J = 2 Hz), 7.11 (1H, d, J = 2 Hz); Mass *m/e*: 242, 244 (M^+). Anal. Calcd for $C_{11}H_{15}OBr$: C, 54.34; H, 6.22. Found: C, 54.51; H, 6.06.

2-Bromo-6-t-butyl-4-ethylphenol (**1b**): pale yellow oil; 61% yield; bp 128°C (6 mm); IR (NaCl): ν_{OH} 3480 cm^{-1}; NMR ($CDCl_3$): δ 1.19 (3H, t, J = 8 Hz), 1.39 (9H, s), 2.54 (2H, q, J = 8 Hz), 5.60 (1H, s, O$\underline{H}$), 6.99 (1H, d, J = 2 Hz), 7.14 (1H, d, J = 2 Hz); Mass *m/e* 256, 258 (M^+). Anal. Calcd for $C_{12}H_{17}OBr$: C, 56.04; H, 6.66. Found: C, 56.28; H, 6.46.

2-Bromo-6-t-butyl-4-isopropylphenol (**1c**): pale yellow oil; 78% yield; bp 135°C (5 mm); IR (NaCl): ν_{OH} 3500 cm^{-1}; NMR ($CDCl_3$): δ 1.21 (6H, d, J = 7 Hz), 1.39 (9H, s), 2.79 (1H, h, J = 7 Hz), 5.60 (1H, s, O$\underline{H}$), 7.04 (1H, d, J = 2 Hz), 7.14 (1H, d, J = 2 Hz); Mass *m/e*: 270, 272 (M^+). Anal. Calcd for $C_{13}H_{19}OBr$: C, 57.57; H, 7.06. Found: C, 57.84; H, 6.86.

2-Bromo-6-t-butyl-4-methoxyphenol (**1d**): yellow oil; 42% yield; bp 125°C (2.5 mm); IR (NaCl): ν_{OH} 3510 cm^{-1}; NMR ($CDCl_3$): δ 1.38 (9H, s), 3.73 (3H, s), 5.39 (1H, s, O$\underline{H}$), 6.78 ~ 6.86 (2H, m); Mass *m/e*: 258, 260 (M^+). Anal. Calcd for $C_{11}H_{15}O_2Br$: C, 50.98; H, 5.83. Found: C, 50.63; H, 5.84.

2-Bromo-4-t-butyl-6-methylphenol (**1e**): colorless prisms (MeOH-H_2O): 72% yield; mp 47 ~ 48°C, bp 135 ~ 137°C (15 mm), lit.$^{7)}$ bp 96°C (3 mm); IR (KBr): ν_{OH} 3490 cm^{-1}; NMR ($CDCl_3$): δ 1.26 (9H, s), 2.27 (3H, s), 5.35 (1H, s, O$\underline{H}$), 7.02 (1H, d, J = 2 Hz), 7.24 (1H, d, J = 2 Hz); Mass *m/e*: 242, 244 (M^+).

2-Bromo-4-t-butyl-6-ethylphenol (**1f**): pale yellow oil; 69% yield; bp 114 ~ 115°C (2.5 mm); IR (NaCl): ν_{OH} 3525 cm^{-1}; NMR ($CDCl_3$): δ 1.23 (3H, t, J = 8 Hz), 1.28 (9H, s), 2.68 (2H, q, J = 8 Hz), 5.36 (1H, br, O$\underline{H}$), 7.05 (1H, d, J = 2 Hz), 7.25 (1H, d, J = 2 Hz); Mass *m/e*: 256, 258 (M^+). Anal. Calcd for $C_{13}H_{17}OBr$: C, 56.04; H, 6.66. Found: C, 56.28; H, 6.51.

2-Bromo-4-t-butyl-6-isopropylphenol (**1g**): pale yellow oil; 71% yield; bp 105 ~ 106°C (1 mm); IR (NaCl): ν_{OH} 3500 cm^{-1}; NMR ($CDCl_3$): δ 1.25 (6H, d, J = 7 Hz), 1.29 (9H, s), 3.47 (1H, h, J = 7 Hz), 6.17 (1H, br, O$\underline{H}$), 7.09 (1H, d, J = 2.5 Hz), 7.24 (1H, d, J = 2.5 Hz); Mass *m/e*: 270, 272 (M^+). Anal. Calcd for $C_{13}H_{19}OBr$: C, 57.57; H, 7.06. Found: C, 57.47; H, 6.94.

2-bromo-4-t-butyl-6-methoxyphenol (**1h**): colorless prisms (hexane); 79% yield; mp 52 ~ 54°C, bp 140 ~ 141°C (2 mm), lit.6) mp 50 ~ 51°C; IR (KBr): ν_{OH} 3520 cm^{-1}; NMR ($CDCl_3$): δ 1.26 (9H, s), 3.86 (3H, s), 5.60 (1H, br, O*H*), 6.78 (1H, d, J = 2 Hz), 3.86 (3H, s), 5.60 (1H, br, O*H*), 6.78 (1H, d, J = 2 Hz), 7.04 (1H, d, J = 2 Hz); Mass *m*/*e*: 258, 260 (M^+).

Chlorination of 2-t-Butyl-4-methylphenol

Typical Procedure

To a solution of 2-t-butyl-4-methylphenol (3.27 g, 20 mmol) in chloroform (30 ml) was added sulfuryl chloride (2.84 g, 21 mmol). After the reaction mixture was stirred for 1 day at room temperature, it was poured into aq. $Na_2S_2O_3$ solution and was extracted with chloroform. The chloroform solution was washed with water, dried over Na_2SO_4, and evaporated *in vacuo* to leave a residue. The residue was distilled under reduced pressure to afford 2.82 g (71%) of **1i**: bp 86 ~ 87°C (2.5 mm); IR (NaCl): ν_{OH} 3550 cm^{-1}; NMR ($CDCl_3$): δ 1.35 (9H, s), 2.21 (3H, s), 5.63 (1H, s, O*H*), 6.89 ~ 6.96 (2H, m); Mass *m*/*e*: 198, 200 (M^+). Anal. Calcd for $C_{11}H_{15}OCl$: C, 66.49; H, 7.61. Found: C, 66.71; H, 7.35.

2-Chloro-4-t-butyl-6-methylphenol (**1j**): colorless oil; 74% yield; bp 90 ~ 91°C (2.5 mm); IR (NaCl): ν_{OH} 3550 cm^{-1}; NMR ($CDCl_3$): δ 1.25 (9H, s), 2.25 (3H, s), 5.42 (1H, s, O*H*), 6.97 (1H, d, J = 2 Hz), 7.08 (1H, d, J = 2 Hz); Mass *m*/*e*: 198, 200 (M^+). Anal. Calcd for $C_{11}H_{15}OCl$: C, 66.49; H, 7.61. Found: C, 66.52; H, 7.52.

Iodination of 4-t-Butyl-2-methylphenol

Typical Procedure

To a solution of 4-t-butyl-2-methylphenol (3.32 g, 20 mmol) and aq. 70% ethylamine solution (15 ml) in ethanol (12 ml) was added a solution of iodine (5.5 g, 21 mmol) and potassium iodide (7 g, 42 mmol) in water (10 ml). After the reaction mixture was stirred for 1 h at room temperature, it was poured into aq. $Na_2S_2O_3$ solution, which was extracted with ether. The ether extract was washed with water, dried over Na_2SO_4, and evaporated *in vacuo* to leave a residue, which was recrystallized from hexane to give **1ℓ**: colorless prisms; yield 4.2 g (73%); mp 82 ~ 83°C; lit.8) 82 ~ 83 °C; IR (KBr): ν_{OH} 3510 cm^{-1}; NMR ($CDCl_3$): δ 1.26 (9H, s), 2.28 (3H, s), 5.10 (1H, s, O*H*), 7.04 (1H, d, J = 2 Hz), 7.40 (1H, d, J = 2 Hz); Mass *m*/*e* 290 (M^+).

2-Iodo-6-t-butyl-4-methylphenol (**1k**): colorless powder; 76% yield; mp 50.5 ~ 52°C, bp 116 ~ 117°C (2.5 mm); IR (KBr): ν_{OH} 3510 cm^{-1}; NMR ($CDCl_3$): δ 1.34 (9H, s), 2.22 (3H, s), 5.28 (1H, s, O*H*), 6.98 (1H, d, J = 2 Hz), 7.29 (1H, d, J = 2 Hz); Mass *m*/*e*: 290

(M^+). Anal. Calcd for $C_{11}H_{15}OI$: C, 45.54; H, 5.21. Found: C, 45.34; H, 5.16.

Oxidation of **1c**

Typical Procedure

To a solution of **1c** (1.08 g, 4 mmol) in benzene (65 ml) was added a solution of $K_3Fe(CN)_6$ (6.5 g, 20 mmol) and KOH (6.5 g, 120 mmol) in water (100 ml), and the mixture was stirred for 20 min at room temperature. The aqueous layer was then removed and the organic layer was washed with water. The organic solution was dried over Na_2SO_4 and evaporated *in vacuo* to leave a residue, which was chromatographed on silica-gel using a mixture of hexane and benzene (1:1) as an eluent to give **7**; pale yellow prisms (hexane); yield 360 mg (34%); mp 131 ~ 133°C (dec.); IR (KBr): ν_{OH} 3500 cm^{-1}; NMR ($CDCl_3$): δ 1.39 (9H, s), 2.06 (3H, s), 4.96 (1H, d, J = 0.5 Hz), 5.21 (1H, d, J = 0.5 Hz), 5.73 (1H, s, O*H*), 7.27 (1H, d, J = 2 Hz), 7.37 (1H, d, J = 2 Hz); Mass *m/e*: 268, 270 (M^+). Anal. Calcd for $C_{13}H_{17}OBr$: C, 58.00; H, 6.37. Found: C, 57.73; H, 6.31. Compounds **8** ~ **14** as well as **7** were isolated by chromatography on silica-gel using the following solvents.

Solvent	Isolated product
hexane:benzene (2:1)	**10**, **11**, **14**
hexane:benzene (1:3)	**13**
benzene	**8**, **9**, **12**

6,6'-Bis(2-t-butyl-*p*-benzoquinone) (**8**): orange needles (hexane); mp 160 ~ 161°C, lit.[9] 161 ~ 162°C; IR (KBr): $\nu_{C=O}$ 1655 cm^{-1}; NMR ($CDCl_3$): δ 1.29 (18H, s), 6.59 ~ 6.65 (4H, m); Mass *m/e*: 326 (M^+).

2,6-Di-t-butyl-8-methoxydibenzofuran-1,4-quinone (**9**): red needles (hexane); mp 178 ~ 180°C, lit.[10] 178 ~ 179°C; IR (KBr): $\nu_{C=O}$ 1665 cm^{-1}; NMR ($CDCl_3$): δ 1.36, 1.48 (each 9H, s), 3.87 (3H, s), 6.56 (1H, s), 6.99 (1H, d, J = 2 Hz), 7.42 (1H, d, J = 2 Hz); Mass *m/e*: 340 (M^+).

4-t-Butyl-2-isopropyl-6-(6-bromo-4-t-butyl-2-isopropylphenoxy)phenol (**10**): pale yellow viscous oil; IR (NaCl): ν_{OH} 3560 cm^{-1}; NMR ($CDCl_3$): δ 1.13, 1.33 (each 9H, s), 1.16, 1.27 (each 6H, d, J = 7 Hz), 2.96 ~ 3.51 (2H, m), 5.69 (1H, br, O*H*), 6.12 (1H, d, J = 2 Hz), 6.81 (1H, d, J = 2 Hz), 7.25 (1H, d, J = 2 Hz), 7.41 (1H, d, J = 2 Hz); Mass *m*/*e*: 460, 462 (M^+). Anal. Calcd for $C_{26}H_{37}O_2Br$: C, 67.67; H, 8.08. Found: C, 67.36; H, 7.82.

4,8-Di-t-butyl-2,6-di-isopropyl-1-hydroxydibenzofuran (**11**): colorless prisms (MeOH-H_2O); mp 153 ~ 155°C; IR (KBr): ν_{OH} 3560 cm^{-1}; NMR ($CDCl_3$): δ 1.35 (6H, d, J = 7 Hz), 1.45 (6H, d, J = 7 Hz), 1.42, 1.58 (each 9H, s), 3.01 ~ 3.51 (2H, m), 5.12 (1H, br, O<u>H</u>), 7.06 (1H, s), 7.22 (1H, d, J = 2 Hz), 7.88 (1H, d, J = 2 Hz); Mass *m*/*e*: 380 (M^+). Anal. Calcd for $C_{26}H_{36}O_2$: C, 82.06; H, 9.54. Found: C, 81.79; H, 9.43.

4-t-Butyl-6-(2-bromo-4-t-butyl-6-methoxyphenoxy)-*o*-benzoquinone (**12**): reddish brown powder; mp 46 ~ 48°C; IR (KBr): $\nu_{C=O}$ 1665 cm^{-1}; NMR ($CDCl_3$): δ 1.09, 1.33 (each 9H, s), 3.79 (3H, s), 5.79 (1H, d, J = 2 Hz), 6.03 (1H, d, J = 2 Hz), 6.92 (1H, d, J = 2 Hz), 7.18 (1H, d, J = 2 Hz); Mass *m*/*e*: 420.093, 422.093 (M^+) (Calcd for $C_{21}H_{25}O_4Br$; 420.094, 422.092).

2-Chloro-4-formyl-6-t-butylphenol (**13**): pale orange prisms (hexane); mp 124 ~ 125°C; IR (KBr): ν_{OH} 3180 cm^{-1}; $\nu_{C=O}$ 1680 cm^{-1}; NMR ($CDCl_3$): δ 1.43 (9H, s), 6.39 (1H, s, O<u>H</u>), 7.67 (1H, d, J = 2 Hz), 7.73 (1H, d, J = 2 Hz), 9.75 (1H, s); Mass *m*/*e*: 212, 214 (M^+). Anal. Calcd for $C_{11}H_{13}O_2Cl$: C, 62.12; H, 6.16. Found: C, 62.42; H, 6.25.

4-t-Butyl-2-methyl-6-(4-t-butyl-6-chloro-2-methylphenoxy)phenol (**14**): pale yellow viscous oil; IR (NaCl): ν_{OH} 3560 cm^{-1}; NMR ($CDCl_3$): δ 1.13, 1.31 (each 9H, s), 2.16, 2.28 (each 3H, s), 5.66 (1H, s, O<u>H</u>), 6.15 (1H, d, J = 2 Hz), 6.74 (1H, d, J = 2 Hz), 7.08 (1H, d, J = 2 Hz), 7.24 (1H, d, J = 2 Hz); Mass *m*/*e*: 360, 362 (M^+). Anal. Calcd for $C_{22}H_{29}O_2Cl$: C, 73.21; H, 8.10. Found: C, 72.87; H, 7.78.

REFERENCES

1) M. Tashiro, H. Yoshiya, and G. Fukata, *J. Org. Chem.*, 1981, **46**, 3784.
2) R. S. Bowman and D. R. Stevens, *J. Org. Chem.*, 1950, **15**, 1172.
3) R. H. Rosenwald, U.S. 2,459,540 (1949); *Chem. Abstr.*, 1949, **43**, 3187e.
4) H. Hart and E. A. Haglund, *J. Org. Chem.*, 1950, **15**, 396.
5) A. Chichibabin, *Compt. Rend.*, 1934, **198**, 1239.
6) R. H. Rosenwald, *J. Amer. Chem. Soc.*, 1952, **74**, 4602.
7) L. E. Mills and C. M. Galloway, U.S. 2,221,808 (1935); *Chem. Abstr.*, 1941, **35**, 1936.
8) D. F. Bowman and F. R. Hewgill, *J. Chem. Soc. [C]*, 1971, 1777.
9) E. C. Horswill and K. U. Ingold, *Canad. J. Chem.*, 1966, **44**, 269.
10) F. R. Hewgill and S. L. Lee, *J. Chem. Soc. [C]*, 1968, 1550.

Received, 16th December, 1982