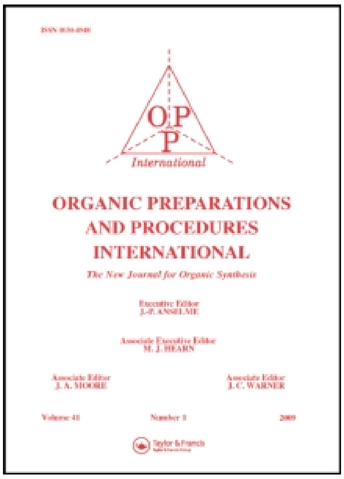

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A PREPARATIVE ROUTE TO ALKOXYPHENOLS USING *t*-BUTYL FUNCTION AS A POSITIONAL PROTECTIVE GROUP

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A PREPARATIVE ROUTE TO ALKOXYPHENOLS USING t-BUTYL FUNCTION AS A POSITIONAL PROTECTIVE GROUP

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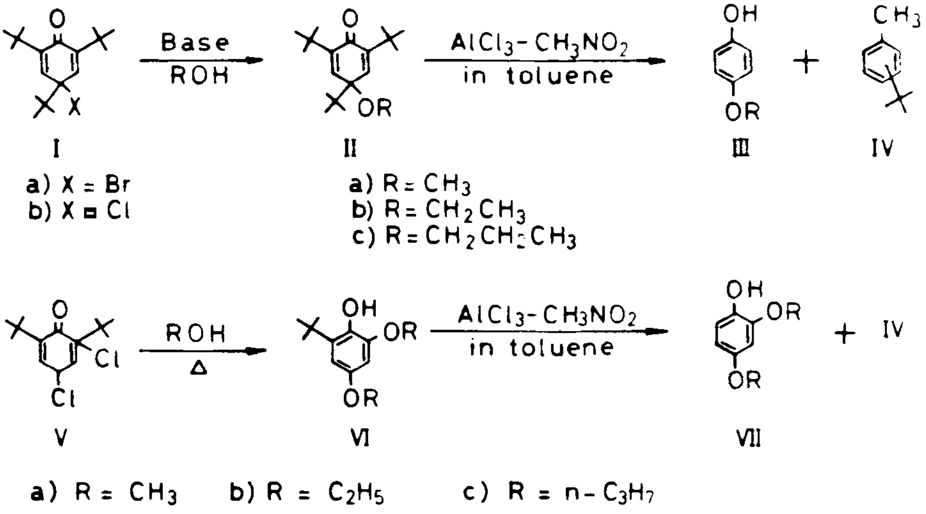
Aryl 4-hydroxyphenyl ethers[1] and 4-aminophenols[2] such as piperidino- and morpholinophenols can be easily prepared by trans-t-butylation or de-t-butylation of the corresponding t-butyl derivatives. The present report describes a preparative route of alkoxyphenols using t-butyl function as a protective group.

Scheme 1



Reaction of 4-bromo-(Ia) and 4-chloro-2,4,6-tri-t-butyl-2,5-cyclohexadien-1-ones (Ib) was carried out in the presence of base and the results are summarized in Table 1.

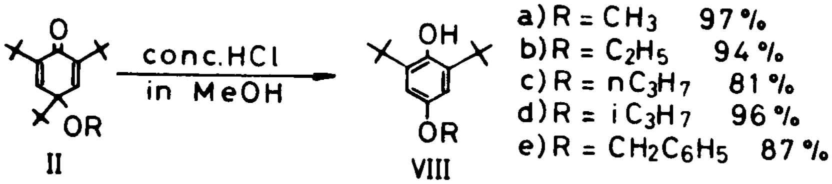
TABLE 1. Reaction of 4-Halo-2,4,6-tri-t-butyl-2,5-cyclohexadienones (Ia-Ib) with Alcohols[a]

Run	ROH	Base	Time (hrs)	Product(%)
1	CH_3	DBU[b]	1	IIa(89)
2	CH_3	pyridine	1	IIa(70)
3	CH_3	α-picoline	1	IIa(94)
4[c]	CH_3	KOH	1	IIa(94)
5	CH_3	α-picoline	1	IIa(99)
6	C_2H_5	DBU	1	IIb(70)
7	C_2H_5	pyridine	1	IIb(62)
8	C_2H_5	α-picoline	1	IIb(95)
9[d]	C_2H_5	KOH	1	IIb(95)
10	C_2H_5	α-picoline	1	IIb(23)
11	$n\text{-}C_3H_7$	α-picoline	1	IIc(94)
12	$n\text{-}C_3H_7$	α-picoline	2	IIc(76)
13	$i\text{-}C_3H_7$	α-picoline	10	IId(78)
14[e]	$i\text{-}C_3H_7$	α-picoline	24	IId(38)
15[f]	CH_2Ph	α-picoline	1	IIe(81)
16[f]	CH_2Ph	α-picoline	1	IIe(81)

a) The dienones were treated with excess refluxing alcohols shown in this Table at reflux until the starting compounds were completely consumed unless otherwise indicated; molar ratio of I:base=1:1. b) DBU: 1,8-diazabicyclo[5.4.0]-7-undecane. c) see ref. 4. d) 2,4,6-Tri-t-butylphenol was obtained as a by-product in 23% yield. e) Compound Ib was recovered in 25% yield. f) Temperature: 115-120° (oil bath).

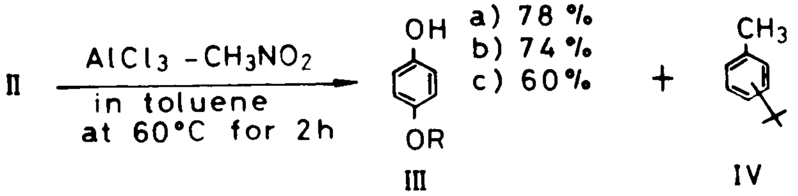
Although the potassium hydroxide-catalyzed reaction of Ia with methanol has been reported to give IIa in 94% yield,[3] a similar treatment of Ia with ethanol gave only a poor yield of IIb. However, organic bases such as DBU, pyridine and α-picoline are found to be suitable catalysts for the conversion of I to II with alcohols, α-picoline being the most effective; treatment of II with conc. HCl in methanol afforded the corresponding 4-alkoxy-2,6-di-*t*-butylphenols (VIII) in good yield (Scheme 2). In the case of IId, the reaction was carried out in *i*-propyl alcohol since in methyl alcohol a mixture of III and IIId (26% and 68%) was obtained.

Scheme 2



The results of the $AlCl_3$-CH_3NO_2-catalyzed trans-*t*-butylation of II in toluene by the reported method[4] are summarized in Scheme 3.

Scheme 3



The reaction of 2,4-dichloro-2,6-di-t-butyl-3,5-cyclohexadien-1-one (V) with alcohols gave 2,4-dialkoxy-6-t-butylphenols (VI) only in the absence of base; in the presence of a base as a catalyst, only IX, X and XI were obtained (Scheme 4, Table 2).

Scheme 4

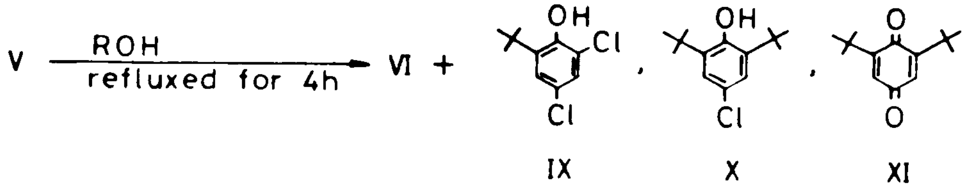


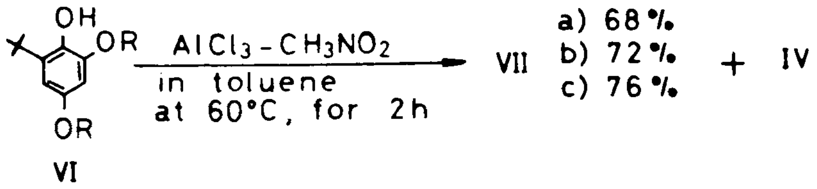
TABLE 2. Reaction of 2,4-Dichloro-2,6-di-t-butyl-3,5-cyclohexadien-1-one (V) with Alcohols[a]

Run	ROH	Base	Product(%)
1	CH_3		VIa(63), X(5), IX(27)
2	CH_3	pyridine	IX(11), X(25), XI(67)
3	C_2H_5		VIb(42), IX(46), X(6)
4	n-C_3H_7		VIc(29), IX(48), XI(17)

a) Reaction condition: refluxed for 4 hrs.

The $AlCl_3$-CH_3NO_2-catalyzed trans-t-butylation of VI in toluene gave the corresponding 2,4-dialkoxyphenols together with IV (Scheme 5).

Scheme 5



EXPERIMENTAL SECTION

All mps are uncorrected. NMR spectra were determined at 100 MHz with a Nihon Denshi JEOL FT-100 NMR spectrometer (TMS as internal reference) and IR spectra were measured as KBr pellets or as liquid film on NaCl plates on a Nippon Bunko IR-A-102 spectrometer. Mass spectra were obtained on a Nihon Denshi JMS-01SA-2 spectrometer at 75 eV by a direct inlet system. The halocyclohexadienones used in the present work were prepared by the reported method.[5] Ia as pale yellow prisms (hexane), mp. 81-82°, lit.[5] mp. 80°. Ib as pale yellow prisms (hexane), mp. 93-94°, lit[5] mp. 94-95°. V as pale yellow prisms (pentane), mp. 63-64°, lit.[6] mp. 64-65°.

Reaction of Halocyclohexadienones with Alcohols. Typical Procedure.- A mixture of 74.5 mg of Ib, 0.5 ml of α-picoline and 10 ml of methanol was refluxed for 2 hrs and then poured into 50 ml of ice-water, and extracted with benzene. The extract was washed with water, dried over Na_2SO_4 and evaporated *in vacuo* to give 71 mg (99%) of IIa. In other cases, the crude products obtained by treatment described above were chromatographed on column of silica gel, if the products contained tarry materials.

IIa as colorless prisms (methanol), mp. 58-59°, lit.[4] mp. 58-59°.

IIb as colorless prisms (methanol/water), mp. 39-40°, lit.[8] mp. 39-41°C.

IIc as colorless oil, IR (NaCl): 1665 and 1640 cm^{-1}; ^1H-NMR (CCl_4): δ 0.95 (9H, s), 0.96 (3H, t, J = 7 Hz), 1.26 (18H, s), 1.55 (2H, sextet, J = 7 Hz), 3.20 (2H, t, J = 7 Hz), and 6.60 (2H, s).

Anal. Calcd. for $C_{21}H_{36}O_2$: C, 78.69; H, 11.32%
Found: C, 78.78; H, 11.25%

IId as pale yellow oil, IR (NaCl): 1665 and 1640 cm^{-1}; ^{1}H-NMR (CCl_4): δ 0.92 (9H, s), 1.11 (6H, d, J = 6.5 Hz), 1.21 (18H, s), 3.36 (1H, heptet, J = 6.5 Hz), and 6.49 (2H, s).

Anal. Calcd. for $C_{21}H_{36}O_2$: C, 78.69; H, 11.32%
Found: C, 78.31; H, 11.36%

IIe as pale yellow oil, IR (NaCl): 1665 and 1640 cm^{-1}; ^{1}H-NMR (CCl_4): δ 0.99 (9H, s), 1.22 (18H, s), 4.35 (2H, s), 6.57 (2H, s), 6.57 (2H, s), 7.30 (5H, s).

Anal. Calcd. for $C_{25}H_{36}O_2$: C, 81.47; H, 9.85%
Found: C, 81.20; H, 9.78%

VIa as pale yellow oil, IR (NaCl): 3530 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.40 (9H, s), 3.74, 3.83 (each 3H, s), 5.56 (1H, broud s, disappeared with D_2O), and 6.37, 6.45 (each 1H, d, J = 2.5 Hz), Mass: m/e 210 (M^+).

Anal. Calcd. for $C_{12}H_{18}O_3$: C, 68.54; H, 8.62%
Found: C, 68.47; H, 8.61%

VIb as colorless prisms (methanol/water), mp 35-38°C, IR (NaCl): 3530 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.39 (9H, s), 1.38 (3H, t, J = 7.0 Hz), 1.44 (3H, t, J = 7.0), 3.96 (2H, q, J = 7 Hz), 4.05 (2H, q, J = 7 Hz), 5.61 (1H, s, disappeared with D_2O), 6.36, 6.43 (each 1H, d, 2.7 Hz); Mass: m/e 238 (M^+).

Anal. Calcd. for $C_{14}H_{22}O_3$: C, 70.56; H, 9.30%
Found: C, 70.75; H, 9.27%

VIc as pale yellow oil, IR (NaCl): 3540 cm^{-1}; ^{1}H-NMR

($CDCl_3$): δ 0.92-1.13 (6H, m), 1.38 (9H, s), 1.56-2.02 (4H, m), 3.84 (2H, t, J = 7.0 Hz), 3.94 (2H, t, J = 7.0), 5.60 (1H, s, disappeared with D_2O), 6.36, 6.43 (each, 1H, d, J = 2.5 Hz); Mass: m/e 266 (M^+).

Anal. Calcd. for $C_{16}H_{26}O_3$: C, 72.14; H, 9.84%.
Found: C, 72.11; H, 9.89%.

Treatment of II with conc.HCl in methanol. General Procedure.- A solution of 4.8 mmol of II and 0.5 ml of conc.HCl in 50 ml of methanol was refluxed for 23 hrs. The reaction mixture was evaporated in vacuo to leave the crude compound (VIII) which was recrystallized. The yields of VIIIa-VIII are shown in Scheme 5.

VIIIa as colorless prisms (methanol/water), mp. 106.5-107.5°, lit.[9] mp. 103-103.5°.

VIIIb as colorless prisms (methanol/water), mp. 83.5-84.5°, IR (KBr): 3600 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.18 (3H, t, J = 7.0 Hz), 1.41 (18H, s), 3.96 (2H, q, J = 7.0 Hz), 4.73 (1H, s, disappeared with D_2O), 6.72 (2H, s); Mass: m/e 250 (M^+).

Anal. Calcd. for $C_{16}H_{26}O_2$: C, 76.75; H, 10.47%.
Found: C, 76.85; H, 10.47%.

VIIIc as colorless prisms (methanol/water), mp. 39.5-40.5°; IR (KBr): 3630 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.04 (2H, t, 6.5 Hz), 1.42 (18H, s), 1.74 (2H, sextet, J = 6.5 Hz), 3.85 (2H, t, J = 6.5 Hz), 4.72 (1H, s, disappeared with D_2O), 6.72 (2H, s); Mass: m/e 264 (M^+).

Anal. Calcd. for $C_{12}H_{28}O_2$: C, 77.22; H, 10.68%.
Found: C, 77.54; H, 10.77%.

VIIId as colorless crystals (it was purified by chromatography on silica gel using hexane as an eluent), mp. 63-65°; IR (KBr): 3590 cm^{-1}; ^1H-NMR ($CDCl_3$): δ 1.30 (6H, d, J = 6.5 Hz), 1.40 (18H, s), 4.40 (1H, heptet, J = 6.5 Hz), 4.74 (1H, s, disappeared with D_2O), 6.72 (2H, s); Mass: m/e 264 (M^+).

Anal. Calcd. for $C_{12}H_{28}O_2$: C, 77.22; H, 10.68%.
Found: C, 77.54; H, 10.77%.

VIIIe as colorless plates (methanol/water), mp. 89.5-90.5°; IR (KBr): 3640 cm^{-1}; ^1H-NMR ($CDCl_3$): δ 1.42 (18H, s), 4.78 (1H, s, disappeared with D_2O), 5.02 (2H, s), 6.88 (2H, s), 7.30-7.55 (5H, m); Mass: m/e 312 (M^+).

Anal. Calcd. for $C_{21}H_{28}O_2$: C, 80.73; H, 9.03%.
Found: C, 80.76; H, 9.12%.

The $AlCl_3$-CH_3NO_2-Catalyzed Trans-t-butylation. Typical Procedure.- A solution of $AlCl_3$ (1.37 g, 10.26 mmol) in CH_3NO_2 (4 ml) was added to a solution of IIa (1 g, 3.42 mmol) in toluene (47 ml) at 60°. The reaction mixture was stirred for 2 hrs at the same temperature then quenched with large excess of ice-water, and extracted with benzene. The benzene solution was extracted with 10% aqueous NaOH (50 ml × 3). The alkali solution was acidified with 10% HCl and extracted with benzene (100 ml × 3). The benzene solution was dried with $NaSO_4$ and evaporated *in vacuo* to afford IIIa as colorless crystals; yield 0.33 g (73%).

IIIa as colorless prisms, mp. 55-56°, lit.[10] mp. 53°C.
IIIb as colorless prisms, mp. 65-65.5°, lit.[11] mp. 66-67°.
IIIc as colorless prisms, mp. 54-55°, lit.[12] 56-57°.

VIIa as pale yellow oil, ^{1}H-NMR ($CDCl_3$): δ 3.72, 3.82 (each 3H, s), 5.20 (1H, broud s, disappeared with D_2O), 6.86 (1H, dd, J = 2.7 and 8.3 Hz), 6.45 (1H, d, J = 2.7 Hz), 6.78 (1H, d, 8.3 Hz); Mass: m/e 154 (M^+).

Anal. Calcd. for $C_8H_{10}O_3$: C, 62.33; H, 6.53%.
Found: C, 61.95; H, 6.58%.

VIIb as colorless needles (hexane), mp. 85.5-86°C; IR (KBr): 3380 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.37 (3H, t, J = 7.0 Hz), 1.43 (3H, t, J = 7.0 Hz), 3.96 (2H, q, J = 7.0 Hz), 4.05 (2H, q, J = 7.0 Hz), 5.24 (1H, broad s, disappeared with D_2O), 6.32 (1H, dd, J = 8.5 and 2.5 Hz), 6.45 (1H, d, J = 2.7 Hz), 6.78 (1H, d, J = 8.5 Hz); Mass: m/e 192 (M^+).

VIIc as pale yellow oil, IR (NaCl): 3450 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 1.02 (6H, t, J = 7.0 Hz), 3.93 (8H, m), 5.24 (1H, s, disappeared with D_2O), 6.34 (1H, dd, J = 8.5 and 2.5 Hz), 6.78 (1H, d, J = 2.5 Hz), 6.46 (1H, d, J = 8.5 Hz); Mass: m/e 210 (M^+).

Anal. Calcd. for $C_{12}H_{18}O_3$: C, 68.55; H, 8.63%.
Found: C, 68.32; H, 8.60%.

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