SHORT PAPER

J. Chem. Research (S),
2000, 582–583

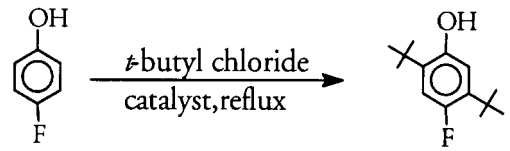
Synthesis of 2,5- and 2,6-di-*t*-butyl-4-halo- or -4-methoxy-phenols using silica, lithium perchlorate and lithium bromide as neutral catalysts†

B. P. Bandgar*, L. S. Uppalla and V. S. Sadavarte

Organic Chemistry Research Laboratory, School of Chemical Sciences, Swami Ramanand Teerth Marathwada University, Vishnupuri, Nanded-431 606, India

When a mixture of 4-halo- or 4-methoxy-phenol and excess of *t*-butyl chloride in the presence of neutral catalyst such as silica or lithium perchlorate or lithium bromide was refluxed, 2,5-and 2,6-di-*t*-butyl-4-halo or 4-methoxy phenols were obtained in good yields.

Synthesis of 2,5-and 2,6-di-*t*-butylated phenols is of great importance because of their usefulness as antioxidants.[1] Generally *t*-butylation of phenols has been carried out using either Lewis acid[1] or Bronsted acid catalysts.[2] Recently, the synthesis of 2,5-di-*t*-butyl-4-fluorophenol has been reported in very poor yield using 4-fluorophenol and *t*-butyl chloride in the presence of $AlCl_3$ as a catalyst.[1] The synthesis of 2,6-di-*t*-butyl-4-fluorophenol using 2,6-di-*t*-butylphenol and expensive xenon difluoride is also described in the literature.[3] More recently an efficient and high yielding synthesis of 2,5-di-*t*-butyl-4-fluorophenol using environmentally friendly catalysts having Lewis acid or Bronsted acid or both characters has been reported.[4] Now we report for the first time the synthesis of 2,5- and 2,6-di-*t*-butyl-4-halo- or -4-methoxy- phenols using neutral catalysts such as silica, lithium perchlorate and lithium bromide.



When a mixture of 4-fluorophenol, excess of *t*-butyl chloride and a catalytic amount of silica or lithium perchlorate or lithium bromide was refluxed, the product formed was only 2,5-di-*t*-butyl-4-fluorophenol in good yield (75–91%, entries 1–3) compared with reported results using $AlCl_3$ as a catalyst[1] which gave only 10.2% yield of the product. The catalysts are removed by simple filtration. Therefore, the present methodology is superior in terms of yields, simplicity of work-up and it is truly catalytic. As the catalysts are neutral and inexpensive, the present method of *t*-butylation is economical as well as eco-friendly as compared with the reported methods using Lewis acid catalyst,[1] Bronsted acid catalyst[2] and xenon difluoride.[3]

It is important to note that mono-*t*-butylated 4-fluorophenol was not formed even in trace amounts. In addition, it is worth commenting that 4-chlorophenol (entries 5–7), 4-bromophenol (entries 8–10) and 4-iodophenol (entries 11–13) on *t*-butylation in the presence of silica, $LiClO_4$ and LiBr gave the corresponding 2,6-di-*t*-butylated phenols and not 2,5-di-*t*-butylated phenols. This is because the steric effect of bulky chloro, bromo and iodo groups at the 4- position did not allow substitution in the 5-position of phenol.

The fluorine 2p orbital of 4-fluorophenol can overlap with the aromatic carbon more effectively than the 3p orbital of chlorine, 4p orbital of bromine, 5p orbital of iodine in 4-chlorophenol, 4-bromophenol and 4-iodophenol respectively.[5,6] Therefore, F is a less deactivating group than Cl, Br or I. However, the electron-withdrawing inductive effect of fluorine makes it deactivating relative to hydrogen.[5,6] The orientation of the *t*-butyl group in 4-fluorophenol is due to the F group whereas the orientation of the *t*-butyl group in 4-chlorophenol, 4-bromophenol and 4-iodophenol is due to the phenolic OH group. The *t*-butylation of 4-fluorophenol gives exclusively 2,5-di-*t*-butyl-4-fluorophenol because of the small size of F, the π-donor effect of F and the 2-*t*-butyl directing effect of an intermediate.

Furthermore, *t*-butylation of 4-methoxyphenol gave a mixture of 2,5-di-*t*-butyl-4-methoxyphenol **(V)** and 2,6-di-*t*-butyl-4-methoxyphenol **(VI)** in a 3:2 ratio. This is because both OH and OMe groups are *o* / *p* orienting and OH is more strongly electron donating than OMe. The 2-*t*-butyl group of the intermediate, 2-*t*-butyl-4-methoxyphenol, is sufficient to direct the second *t*-butyl group to the 5-position. As the catalysts used here are neutral, the most important advantage of this methodology is to carry out *t*-butylation of complex phenol molecules having acid sensitive functional groups. An attempt to carry out *t*-butylation of 4-fluorophenol in the absence of these catalysts failed (entry 4).

Experimental

^1H NMR and ^{13}C NMR spectra were obtained from a 200 MHz instrument whereas IR spectra were recorded on a Bomem MB104 FT-IR spectrometer. Neutral silica gel G, $LiClO_4$ and LiBr were obtained from Lancaster, UK.

*Preparation of 2,5-di-*t*-butyl-4-fluoropheno:* A mixture of 4-fluorophenol (5 mmol), *t*-butyl chloride (10 ml) and catalyst, silica or $LiClO_4$ or LiBr (100 mg) was refluxed for specified time (Table). After completion of the reaction (TLC), the catalyst was filtered off and washed with dichloromethane (4 × 10 ml). The solvent was removed under vacuum and the crude product was purified by column chromatography (pet. ether : ethylacetate = 9:1 as an eluent).

*2,5-Di-*t*-butyl-4-fluorophenol* **(I)**: m.p. = 92–93°C (lit.[1] = 92–93°C); IR : 1210, 1500, 1610, 3550cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 1.32 (s, 9H, 3 × CH_3), 1.39 (s, 9H, 3 × CH_3), 4.91 (s, 1 H, OH), 6.65 (d, *J* = 8.5 Hz, 1H, Ar-H), 6.92 (d, *J* = 15.8 Hz, 1 H, Ar-H); ^{13}C NMR (50 MHz) : δ = 28.7, 29.5, 33.1, 34.3, 114.6, 115.6, 134.3, 135.1 149.6, 156 ppm. MS (70 eV) = *m/z* (%) = 224.3 (57); 57.04 (100). Anal. calc. for $C_{14}H_{21}FO$ (224.3) : C, 74.96; H,9.37; F, 8.48; Found: C, 75.06; H, 9.29; F, 8.39.

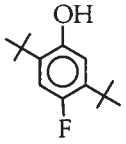
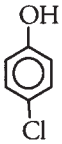
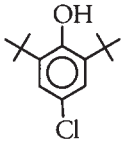
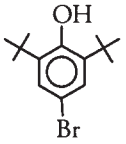
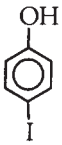
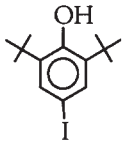
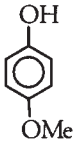
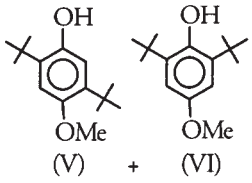
*2,6-Di-*t*-butyl-4-chlorophenol* **(II)**: b.p. = 247–248 0C/760 mm of Hg; IR : 1210, 1500, 1600, 3570 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 1.33 (s, 18 H, 6 x CH_3), 5.19 (s, 1 H, OH), 7.2 (s, 2 H, Ar–H); ^{13}C NMR (50 MHz) : δ = 25.2, 35.4, 112.4, 116.3, 130.7, 141.2. MS (70 eV) = *m/z* (%) = 240.5 (71.2), 57.04 (100). Anal. calc. for $C_{14}H_{21}ClO$ (240.5) : C, 69.85; H, 8.73; Cl, 14.76; Found C, 69.79; H, 8.81; Cl, 14.69.

*2,6-Di-*t*-butyl-4-bromophenol* **(III)**: m.p. = 80–81 °C (Lit[7] m.p. = 78–83 °C); IR = 1190, 1490, 1600, 3580 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 1.31 (s, 18H, 6 × CH_3), 4.8 (s, 1 H, OH), 6.9 (s, 2 H,

* To receive any correspondence. E-mail: upekam@hotmail.com

† This is a Short Paper, there is therefore no corresponding material in *J Chem. Research (M).*

Table 1 *t*-Butylation of phenols using silica, lithium perchlorate and lithium bromide

Entry	Phenol	Catalyst	Product	Reaction time/h	Yield/%
1		Silica	 (I)	2.5	75
2		$LiClO_4$		0.75	89
3		LiBr		1.00	91
4		None		6.00	0.0
5		Silica	 (II)	2.5	79
6		$LiClO_4$		0.75	89
7		LiBr		0.80	88
8		Silica	 (III)	2.55	78
9		$LiClO_4$		0.80	82
10		LiBr		0.80	87
11		Silica	 (IV)	3.00	69
12		$LiClO_4$		0.80	66
13		LiBr		0.80	61
14		Silica	 (V) + (VI) 3:2	2.5	68
15		$LiClO_4$		0.90	79
16		LiBr		1.00	86

Ar–H); ^{13}C ^{13}C NMR (50 MHz): δ = 20.7, 32.1, 114.6, 115.2, 128.3, 137.2. MS (70 eV) = *m/z* (%) = 285.14 (45), 57.04 (100). Anal. calc. for $C_{14}H_{21}BrO$ (285.14): C, 58.94; H, 7.3; Br, 28.07; Found: C, 58.91 H, 7.38; Br, 28.16

2,6-Di-t-butyl-4-iodophenol **(IV)**: m.p. = 109–110 °C; IR: 1200, 1500, 1600, 3560 cm^{-1}; ^1H-NMR (200MHz, $CDCl_3$): δ = 1.30 (s, 18 H, 6 × CH3), 4.8 (s, 1 H, OH), 6.9 (s, 2H, Ar–H); ^{13}C NMR (50 MHz): δ = 21.4, 30.9, 111.4, 113.3, 125.4, 132.1. MS (70 EV) = *m/z* (%) =332.14 (43.2), 57.04 (100). Anal. calc. for $C_{14}H_{21}IO$ (332): C, 50.60; H, 6.32; I, 38.2; Found: C, 50.71; H, 6.40; I, 38.18.

2,5-Di-t-butyl-4-methoxyphenol **(V)**: m.p. = 102–103 °C (Lit[7]m.p. = 99–102 °C); IR : 1205, 1480, 1590, 3540 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 1.33 (s, 9H, 3 × CH_3), 1.39 (s, 9H, 3 × CH_3), 4.15 (s, 3H, OMe) 4.52 (s, 1 H, OH), 6.85(m, 2 H, Ar–H); ^{13}C NMR (50 MHz): δ=24.7, 25.2, 35.1, 36.2, 60.3, 114.2, 115.6, 134.7, 135.2, 141.9, 144.4. MS (70 EV) = *m/z* (%) =236.15 (100). Anal. calc. for $C_{15}H_{24}O_2$ (236.15) : C, 76.27; H, 10.16; Found : C, 76.21; H, 10.11

2,6-Di-t-butyl-4-methoxyphenol **(VI)**: m.p. = 104–105 °C (Lit[7]m.p. = 105–106 °C); IR : 1200, 1490, 1600, 3550 cm^{-1}; ^1H-NMR (200 MHz, $CDCl_3$) : δ = 1.31 (s, 18H, 6 × CH_3), 4.2 (s, 3H, OMe), 4.6 (s, 1 H, OH), 7.1(s, 2H, Ar–H); ^{13}C NMR (50 MHz): δ = 24.9, 33.7, 58.4, 110.7, 114.1, 127.3, 136.4. MS (70 eV) = *m/z* (%) = 236.15 (56), 57.04 (100). Anal. calc. for $C_{15}H_{24}O_2$ (236.15): C, 76.27; H, 10.16; Found : C, 76.18; H, 10.21

VSS thanks CSIR, New Dehli for Jr. Research Fellowship.

Received 23 April 2000; accepted 15 November 2000
Paper 00/293

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