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An Efficient Synthetic Route to Novel 3-Alkyl- and 3-Aryl-4-iodophenols

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Abstract: An efficient method for the preparation of novel 3-alkyl- and 3-aryl-4-iodophenols from 3-alkyl- and 3-arylphenols is described.

Key words: phenols, halogenation, deiodination, iodine monochloride, Suzuki reaction

As part of an ongoing project it was necessary to access a series of novel 4-arylphenols containing sterically demanding functionality at the 3-position; in particular phenols with isopropyl, *tert*-butyl, and phenyl groups were of interest for our work. A viable approach to these compounds via palladium-catalysed coupling of the 3-alkyl- and 3-aryl-4-halophenols **1** (Figure 1) was proposed. However, literature searches revealed a paucity of information regarding the synthesis of these 4-halogenated 3-alkyl- and 3-arylphenols.

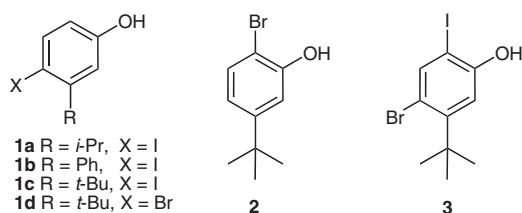


Figure 1

A few methods have been reported for the direct *para*-iodination of phenols;¹ these include the use of sodium iodide/Chloramine T, iodine/*tert*-butyl hypochlorite, and iodine in trimethyl phosphate. Reagents such as iodine/potassium iodate,² bis(pyridine)iodonium tetrafluoroborate,³ or potassium iodide/Oxone⁴ are also commonly used. However, none of these methods refers to examples wherein phenols bearing a 3-alkyl or 3-aryl substituent and unsubstituted *ortho*-position(s) are directly and selectively *para*-iodinated.

This paper describes a procedure for selectively and efficiently preparing the 4-halogenated compounds **1** from 3-alkyl- and 3-arylphenols.

Initial attempts were undertaken following a literature procedure⁵ for the preparation of 4-iodophenols that are

unsubstituted in the 3-position, utilising one equivalent of sodium iodide and sodium hypochlorite in the presence of sodium hydroxide in an aqueous methanolic solution.

When this method was applied to the alkyl-substituted 3-isopropylphenol (**4a**) the main product was 2-iodo-5-isopropylphenol (**5a**) with 2,4-diiodo-5-isopropylphenol (**6a**) as a byproduct (Table 1). However, by changing to acidic conditions and using one equivalent of iodine monochloride in methanol the reactivity of the phenol was decreased and 4-iodo-3-isopropylphenol (**1a**) and the 2-iodo isomer **5a** were obtained in good isolated yield accompanied by a minor amount of 2,4-diiodo-5-isopropylphenol (**6a**) (Table 1).

Table 1 Iodination of 3-Substituted Phenols **4a–c** with Iodine Monochloride in Methanol

1,4-6	R	Yield (%)	
		1	5
a	<i>i</i> -Pr	41	28
b	Ph	12	62
c	<i>t</i> -Bu	0	86

Isomers **1a** and **5a** were separated by column chromatography and analysed by LCMS and NMR. NOE experiments provided definite characterisation of the isomers. Compound **1a** showed one NOE signal between the aryl proton H2 and the adjacent isopropyl group protons; compound **5a** showed two NOE signals between the isopropyl group protons and the adjacent aryl protons H4 and H6.

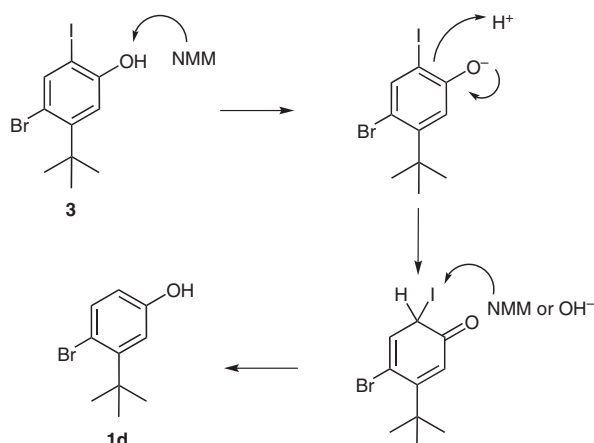
A similar result was obtained when biphenyl-3-ol (**4b**) was iodinated with one equivalent of iodine monochloride in methanol under acidic conditions. A mixture of 6-iodobiphenyl-3-ol (**1b**) and 4-iodobiphenyl-3-ol (**5b**) was formed (Table 1) and the isomers were also separated by column chromatography and characterised by LCMS and NMR and the structure assigned by NOE.

Applying the same method to the sterically most hindered 3-*tert*-butylphenol (**4c**), the sole product isolated was 5-

tert-butyl-2-iodophenol (**5c**)⁶ with none of the desired isomer **1c**.

It was therefore necessary to pursue another approach towards this template and attention was turned to the preparation of 4-bromo-3-*tert*-butylphenol (**1d**) (Figure 1). It appeared likely that **1d** could be prepared by the selective dehalogenation of a 2,4-dihalophenol following a literature procedure.⁷ Thus 5-*tert*-butyl-2-iodophenol (**5c**) was brominated with bromine in carbon tetrachloride to provide 4-bromo-5-*tert*-butyl-2-iodophenol (**3**). Compound **3** was subsequently deiodinated under reductive conditions using either zinc in 10% hydrochloric acid and ethanol or zinc in 10% aqueous sodium hydroxide solution. In our hands these dehalogenation conditions did not lead to the reported⁷ 4-bromo-3-*tert*-butylphenol (**1d**). The product isolated under acidic and basic conditions was 2-bromo-5-*tert*-butylphenol (**2**) (Figure 1) and the structure was confirmed by NOE. It appears that under the applied reductive conditions selective deiodination takes place with concomitant migration of bromine. An alternative literature method⁸ whereby 3-*tert*-butylphenol (**4c**) was esterified with boric acid and subsequently brominated with bromine in chloroform also failed to produce the reported isomer **1d**; the undesired isomer **2** was isolated instead.

Finally, deiodination of **3** under nonreductive conditions⁹ using *N*-methylmorpholine afforded the desired 4-bromo-3-*tert*-butylphenol (**1d**). *N*-Methylmorpholine initiates the selective removal of iodine, the bromo functionality remains unreacted and no migration of the bromine substituent is observed. Mechanistically the deiodination can be rationalised as proposed by Talekar et al.⁹ (Scheme 1); however the fate of the iodine moiety remains somewhat unclear. It also has to be noted that traces of water are essential to the reaction, allowing for hypoiodic acid as a possible temporary intermediate.



Scheme 1 Mechanism for the deiodination with *N*-methylmorpholine proposed by Talekar et al.⁹

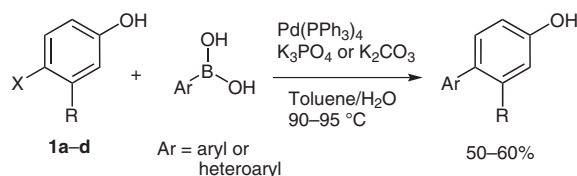
Following the success of this approach for the preparation of 4-bromophenol **1d**, a more efficient procedure for the preparation of 4-iodophenols **1a–c** was developed. Diiodination of compounds **4a–c** with iodine monochloride was

achieved under basic conditions to give products **6a–c** (Table 2). Subsequent selective *ortho*-deiodination with *N*-methylmorpholine⁹ furnished the desired products **1a–c** in good yields.

Table 2 Diiodination of Phenols **4a–c** and Selective *ortho*-Deiodination of **6a–c**

1,4,6	R	Yield (%)	
		6	1
a	<i>i</i> -Pr	60	74
b	Ph	58	37
c	<i>t</i> -Bu	99	51

4-Iodo- and 4-bromophenols **1a–d** were subjected to standard Suzuki reaction conditions using a range of aryl- and heteroarylboronic acids (Scheme 2). Tetrakis(triphenylphosphine)palladium(0) was the preferred catalyst in the presence of tripotassium phosphate or potassium carbonate, in a mixture of toluene–water (9:1) at 90–95 °C; typically yields of 50–60% were obtained. As expected the 4-bromophenol **1d** was less reactive than the corresponding 4-iodophenol **1c**.



Scheme 2 Palladium-catalysed coupling reactions of 4-halophenols **1a–d** with boronic acids

In summary an efficient and high yielding method towards the synthesis of 3-alkyl- and 3-aryl-4-iodophenols is described. This requires a diiodination step followed by selective monodeiodination under nonreductive conditions. These novel compounds are suitable building blocks for palladium-catalysed coupling reactions under standard conditions.

Reagents and solvents were purchased from Acros, Aldrich, or Alfa Aesar and used without further purification. Flash column chromatography was performed on silica gel 60 Å, Davisil, 35–70 micron (Fisher Scientific). TLC was performed on silica gel 60 F₂₅₄ plates (Merck) and visualised with UV-light 254 nm. ¹H NMR, ¹³C NMR, and NOE spectra were recorded on a Jeol ECA 500 instrument. HPLC/MS data were obtained using an HP1100 LC combined with a Waters Micromass ZMD mass spectrometer operating in positive and negative ion mode. HRMS data were obtained using a VG Autospec instrument with a resolution <5000 ppm in EI mode.

4-Iodo-3-isopropylphenol (1a) and 2-Iodo-5-isopropylphenol (5a)

To a stirred soln of commercially available 3-isopropylphenol (**4a**, 10.0 g, 73.4 mmol) in MeOH (250 mL) was added a soln of ICl (11.9 g, 73.4 mmol) in MeOH (100 mL) over 1 h. After stirring at r.t. for 16 h, the mixture was quenched with 20% aq Na₂S₂O₃ (50 mL), stirred for 20 min, and concentrated to give a two-phase mixture. H₂O (200 mL) was added and the mixture was extracted with EtOAc (2 × 150 mL). The combined organic phases were dried (MgSO₄), filtered, and concentrated to dryness. The crude product was purified by column chromatography (silica gel, gradient hexane to hexane–CH₂Cl₂, 1:1).

4-Iodo-3-isopropylphenol (1a)

Yield: 7.88 g (41%); *R_f* = 0.26 (hexane–CH₂Cl₂, 2:3).

¹H NMR (500 MHz, CDCl₃): δ = 7.63 (d, *J* = 8.5 Hz, 1 H, H5), 6.76 (d, *J* = 3.5 Hz, 1 H, H2), 6.43 (dd, *J* = 3, 8.5 Hz, 1 H, H6), 4.69 (s, 1 H, OH), 3.12 (sept, *J* = 7 Hz, 1 H, CH), 1.21 (d, *J* = 7 Hz, 6 H, CH₃); NOE cross peaks observed: H2 to δ = 1.21.

¹³C NMR (125 MHz, CDCl₃): δ = 156.11, 151.96, 140.03, 115.24, 113.42, 89.51, 37.94, 22.95.

HPLC/MS: *m/z* = 261 (M⁻).

Anal. Calcd for C₉H₁₁IO: C, 41.25; H, 4.23. Found: C, 41.35; H, 4.19.

2-Iodo-5-isopropylphenol (5a)

Yield: 5.34 g (28%); *R_f* = 0.54 (hexane–CH₂Cl₂, 2:3);

¹H NMR (500 MHz, CDCl₃): δ = 7.54 (d, *J* = 8 Hz, 1 H, H3), 6.88 (d, *J* = 2 Hz, 1 H, H6), 6.57 (dd, *J* = 2.5, 8.5 Hz, 1 H, H4), 5.18 (s, 1 H, OH), 2.83 (sept, *J* = 7 Hz, 1 H, CH), 1.22 (d, *J* = 7 Hz, 6 H, CH₃); NOE cross peaks observed: H4 and H6 to δ = 1.22.

¹³C NMR (125 MHz, CDCl₃): δ = 154.67, 151.95, 137.83, 120.99, 113.23, 81.92, 33.75, 23.75.

HPLC/MS: *m/z* = 261 (M⁻).

HRMS: *m/z* calcd for C₉H₁₁IO: 261.9854; found: 261.9846.

Anal. Calcd for C₉H₁₁IO: C, 41.25; H, 4.23. Found: C, 41.71; H, 4.34.

6-Iodobiphenyl-3-ol (1b) and 4-Iodobiphenyl-3-ol (5b)

A soln of ICl (2.28 g, 14.1 mmol) in MeOH (10 mL) was added dropwise to a stirred soln of commercially available biphenyl-3-ol (**4b**, 2.00 g, 11.7 mmol) in MeOH (40 mL) over 1 h. The mixture was stirred at r.t. for 20 h, quenched with 20% Na₂S₂O₃ soln (30 mL) and stirred for a further 15 min. The mixture was concentrated under vacuum to half of its volume and extracted with EtOAc (2 × 100 mL). The combined organic phases were dried (Na₂SO₄), filtered, and concentrated under vacuum to dryness. The resulting oil was purified by chromatography (silica gel, hexane–CH₂Cl₂, 4:1 to 100% CH₂Cl₂).

6-Iodobiphenyl-3-ol (1b)

Yield: 0.41 g (12%); *R_f* = 0.20 (hexane–CH₂Cl₂, 4:1).

¹H NMR (500 MHz, CDCl₃): δ = 7.76 (d, *J* = 8.5 Hz, 1 H, H5), 7.39–7.43 (m, 3 H, H_{aryl}), 7.31–7.33 (m, 2 H, H_{aryl}), 6.83 (d, *J* = 3 Hz, 1 H, H2), 6.59 (dd, *J* = 8.5, 3 Hz, 1 H, H6) 4.77 (s, 1 H, OH); NOE cross peaks observed: H2 to δ = 7.31–7.33.

¹³C NMR (125 MHz, CDCl₃): δ = 155.63, 147.79, 143.75, 140.27, 129.11, 127.97, 127.77, 117.47, 116.41, 87.19.

HPLC/MS: *m/z* = 295 (M⁻).

HRMS: *m/z* calcd for C₁₂H₉IO: 295.9698; found: 295.9706.

Anal. Calcd for C₁₂H₉IO: C, 48.68; H, 3.06. Found: C, 49.26; H, 3.06.

4-Iodobiphenyl-3-ol (5b)

Yield: 2.15 g (62%); *R_f* = 0.43 (hexane–CH₂Cl₂, 4:1).

¹H NMR (500 MHz, CDCl₃): δ = 7.70 (d, *J* = 8 Hz, 1 H, H3), 7.55–7.58 (m, 2 H, H_{aryl}), 7.42–7.45 (m, 2 H, H_{aryl}), 7.35–7.38 (m, 1 H, H_{aryl}), 7.23 (d, *J* = 2 Hz, 1 H, H6), 6.93 (dd, *J* = 8, 2.5 Hz, 1 H, H4), 5.30 (s, 1 H, OH); NOE cross peaks observed: H4 and H6 to δ = 7.55–7.58.

¹³C NMR (125 MHz, CDCl₃): δ = 155.07, 143.75, 139.74, 138.38, 128.87, 127.87, 126.95, 121.34, 113.69, 84.33.

HPLC/MS: *m/z* = 295 (M⁻).

Anal. Calcd for C₁₂H₉IO: C, 48.68; H, 3.06. Found: C, 48.65; H, 2.99.

3-tert-Butyl-4-iodophenol (1c); Typical Procedure

A soln of 5-*tert*-butyl-2,4-diiodophenol (**6c**, 2.63 g, 6.54 mmol) in NMM (27 mL) was heated to reflux for 8 h. The mixture was concentrated under vacuum. The residues were taken up in EtOAc (50 mL) and washed with 2 M HCl (25 mL) and 20% Na₂S₂O₃ soln (30 mL). The organic phase was dried (MgSO₄), filtered, and concentrated under vacuum. The resulting oil was purified by column chromatography (hexane–CH₂Cl₂, 7:3 to 1:1); yield: 922 mg (51%); *R_f* = 0.42 (hexane–CH₂Cl₂, 3:7).

¹H NMR (500 MHz, CDCl₃): δ = 7.79 (d, *J* = 8 Hz, 1 H, H5), 6.94 (d, *J* = 3 Hz, 1 H, H2), 6.38 (dd, *J* = 2.9, 8.4 Hz, 1 H, H6), 4.65 (s, 1 H, OH), 1.50 (s, 9 H, CH₃); NOE cross peaks observed: H2 to δ = 1.50.

¹³C NMR (125 MHz, CDCl₃): δ = 155.33, 151.93, 144.17, 115.50, 114.69, 83.49, 36.56, 29.70.

HPLC/MS: *m/z* = 275 (M⁻).

Anal. Calcd for C₁₀H₁₃IO: C, 43.50; H, 4.75. Found: C, 43.42; H, 4.68.

4-Bromo-3-tert-butylphenol (1d)

4-Bromo-5-*tert*-butyl-2-iodophenol (**3**,⁷ 100 mg, 0.281 mmol) was taken up in NMM (2 mL) and heated to reflux for 16 h. The soln was cooled to r.t. and concentrated to dryness. The obtained oil was taken up in EtOAc (50 mL) and washed with 2 M HCl (20 mL). The organic phase was dried (MgSO₄), filtered, and concentrated to dryness. The resulting oil was purified by chromatography (silica gel, hexane–CH₂Cl₂, 9:1 to 1:1); yield: 34 mg (50%); *R_f* = 0.20 (hexane–CH₂Cl₂, 1:1).

¹H NMR (500 MHz, CDCl₃): δ = 7.42 (d, *J* = 8.5 Hz, 1 H, H5), 6.93 (d, *J* = 2.5 Hz, 1 H, H2), 6.53 (dd, *J* = 8.5, 2.5 Hz, 1 H, H6), 4.68 (s, 1 H, OH), 1.48 (s, 9 H, CH₃); NOE cross peaks observed: H2 to δ = 1.48.

2-Bromo-5-tert-butylphenol (2)

4-Bromo-5-*tert*-butyl-2-iodophenol (**3**,⁷ 1.97 g, 5.56 mmol) was taken up in 10% aq NaOH (80 mL). Zn powder (4.36 g, 66.7 mmol) was added in 1 portion and the resulting suspension was heated to 100 °C for 2.5 h. The mixture was cooled to r.t. and filtered through a pad of Celite. The filtrate was acidified to pH 1–2 with concd HCl and extracted with EtOAc (2 × 100 mL). The combined organic layers were dried (MgSO₄), filtered, and concentrated to dryness. The resulting oil was purified by chromatography (silica gel, hexane–Et₂O, 95:5 to 4:1); yield: 1.27 g (quantitative); *R_f* = 0.51 (hexane–Et₂O, 4:1).

¹H NMR (500 MHz, CDCl₃): δ = 7.35 (d, *J* = 8.5 Hz, 1 H, H3), 7.06 (d, *J* = 2.5 Hz, 1 H, H6), 6.84 (dd, *J* = 8.5, 2.5 Hz, 1 H, H4), 5.41 (s, 1 H, OH), 1.29 (s, 9 H, CH₃); NOE cross peaks observed: H4 and H6 to δ = 1.29.

5-tert-Butyl-2-iodophenol (5c); Typical Procedure^{6,7}

A soln of ICl (1.07 g, 6.60 mmol) in MeOH (15 mL) was added dropwise to a stirred soln of commercially available 3-tert-butylphenol (**4c**, 1.00 g, 6.60 mmol) and NaOH (266 mg, 6.60 mmol) in MeOH (20 mL). The mixture was stirred at r.t. for 19 h, quenched with 20% Na₂S₂O₃ soln (25 mL), and stirred for a further 15 min. The mixture was concentrated under vacuum to give a two-phase mixture. 2 M HCl (20 mL) was added and the mixture was extracted with EtOAc (2 × 50 mL). The combined organic phases were dried (MgSO₄), filtered, and concentrated under vacuum. The resulting oil was purified by column chromatography (silica gel, hexane and a gradient of hexane to hexane–EtOAc, 97:3); yield: 1.59 g (86%); *R*_f = 0.29 (hexane–EtOAc, 9:1).

¹H NMR (500 MHz, CDCl₃): δ = 7.54 (d, *J* = 8 Hz, 1 H, H₃), 7.04 (d, *J* = 2 Hz, 1 H, H₆), 6.73 (dd, *J* = 2.5, 8.5 Hz, 1 H, H₄), 5.18 (s, 1 H, OH), 1.28 (s, 9 H, CH₃); NOE cross peaks observed: H₄ and H₆ to δ = 1.28.

¹³C NMR (125 MHz, CDCl₃): δ = 154.45, 154.34, 137.52, 119.96, 112.52, 81.75, 34.63, 31.12.

HPLC/MS: *m/z* = 275 (M⁻).

Anal. Calcd for C₁₀H₁₃IO: C, 43.50; H, 4.75. Found: C, 43.52; H, 4.68.

2,4-Diiodo-5-isopropylphenol (6a)

Following the typical procedure for **5c** using 3-isopropylphenol (**4a**, 20.0 g, 147 mmol) with ICl (47.7 g, 294 mmol) in MeOH in the presence of NaOH (11.8 g, 294 mmol), the product was isolated after column chromatography (hexane–CH₂Cl₂, 4:1 to CH₂Cl₂) as a beige-coloured solid; yield: 34.1 g (60%); *R*_f = 0.45 (hexane–CH₂Cl₂, 1:1).

HPLC/MS: *m/z* = 387 (M⁻).

4,6-Diiodobiphenyl-3-ol (6b)

Following the typical procedure for **5c** using biphenyl-3-ol (**4b**, 600 mg, 3.53 mmol) with ICl (1.14 g, 7.05 mmol) in MeOH in the presence of NaOH (282 mg, 7.05 mmol), the product was isolated after column chromatography (hexane–CH₂Cl₂, 4:1 to CH₂Cl₂) as a colourless oil; yield: 864 mg (58%); *R*_f = 0.49 (hexane–CH₂Cl₂, 1:1).

HPLC/MS: *m/z* = 421 (M⁻).

5-tert-Butyl-2,4-diiodophenol (6c)

Following the typical procedure for **5c** using 3-tert-butylphenol (**4c**, 5.00 g, 33.3 mmol) with ICl (12.2 g, 75.2 mmol) in MeOH in the presence of NaOH (4.33 g, 108 mmol), the product was isolated as a beige-coloured solid without purification; yield: 13.3 g (99%).

For analytical purposes a sample was purified by column chromatography (silica gel, hexane–CH₂Cl₂, 8:2 to 7:3); *R*_f = 0.27 (hexane–CH₂Cl₂, 7:3).

¹H NMR (500 MHz, CDCl₃): δ = 8.19 (s, 1 H, H_{aryl}), 7.09 (s, 1 H, H_{aryl}), 5.15 (s, 1 H, OH), 1.49 (s, 9 H, CH₃).

¹³C NMR (125 MHz, CDCl₃): δ = 154.94, 152.92, 150.26, 114.76, 83.76, 83.15, 36.57, 29.57.

HPLC/MS: *m/z* = 401 (M⁻).

HRMS: *m/z* calcd for C₁₀H₁₂I₂O: 401.8977; found: 401.8962.

Anal. Calcd for C₁₀H₁₂I₂O: C, 29.88; H, 3.01. Found: C, 30.63; H, 3.06.

Suzuki Reaction

The phenol building block **1a–d** (0.54 mmol) was taken up in toluene (8–10 mL), boronic acid (1.08 mmol) was added, followed by K₃PO₄ (1.08 mmol), Pd(PPh₃)₄ (63 mg, 10 mol%), and H₂O (1–2 mL). The mixture was heated to 90–95 °C for 14–16 h. The mixture was filtered through a pad of Celite. After concentration of the filtrate the crude mixture was purified by column chromatography (hexane–CH₂Cl₂, 9:1 to 6:4).

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