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Regioselective iodination of phenol and analogues using *N*-iodosuccinimide and *p*-toluenesulfonic acid

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ABSTRACT

Mild and highly regioselective monoiodination of phenol and analogues is achieved in high to excellent yields at room temperature with a combination of stoichiometric *p*-toluenesulfonic acid and *N*-iodosuccinimide.

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Iodination of phenols furnishes important synthetic intermediates¹ which are useful in a variety of palladium-catalysed and copper(I)-assisted reactions, such as the Heck, Stille and the Ullmann reactions.² Iodophenol compounds are also constituents of various naturally occurring biologically active compounds, especially those of marine sponge metabolites.³ Numerous methods exist for direct iodination of phenols which include NaClO₂-NaI-HCl,^{4a} ICl,^{4b} I₂tetrabutylammonium peroxydisulfate,^{4c} bis(*sym*-collidine)iodine(I) hexafluorophosphate,^{4d} benzyltrimethylammonium dichloroiodate,^{4e} chloramine T-Nal^{4f} and Nal-tert-butyl hypochlorite.^{4g} Previous regioselective phenol iodinations employed various combinations of reagents, that include I_2 -cerium ammonium nitrate, ^{5a} I_2 - β cyclodextrin,^{5b} TlOAc-I₂^{5c} and KI-benzyltriphenylphosphonium peroxymonosulfate.^{5d} While several methods to achieve ortho-iodination have been established, ^{5a-c} high yielding *para*-selective iodination of phenol and analogues remains a challenge.

As part of our continuing efforts to synthesise L-thyronine analogues, via L-tyrosine and *para*-iodophenol derivative copper(I)-assisted coupling reactions, we were obliged to seek a mild, facile and highly regioselective methodology for the synthesis of halogenated analogues of *p*-iodophenol, such as 6-bromo-2chloro-4-iodophenol. A potential source of iodonium ions, other than molecular iodine itself, is *N*-iodosuccinimide (NIS). The use of NIS in aromatic electrophilic iodination has been amply demonstrated in deactivated and activated aromatic systems using various NIS-activating co-reagents, such as CF₃SO₃H (as solvent for deactivated systems),^{6a} catalytic hydroxy(tosyloxy)iodobenzene (HTIB),^{6b} catalytic *p*-toluenesulfonic acid (*p*TsOH),^{6c} CH₃CN (as solvent for the activated systems)^{6d} and catalytic CF₃CO₂H.^{6e} Herein the combination of *p*TsOH and NIS, previously demonstrated in the iodination of polyalkylbenzenes,^{6c} and recently in the syntheses of 3-iodo and 3-halo-5-iodo analogues of *N*-acetyl-L-tyrosine,^{6f} was found to give, at ambient temperature, highly regioselective monoiodination of phenol and its analogues in high to excellent yields.

Using 1 equiv of *p*TsOH and NIS in acetonitrile, phenol (1) was converted, after 14 h of stirring at room temperature, to 4-iodophenol (1a) in 95% yield (Table 1, entry 1b). Acids other than pTsOH were also investigated for their promoting effect on the selectivity of para-iodination of phenol. With 1 equiv of CH₃CO₂H, the yield and selectivity of 1a were 14% and 16%, respectively. With 1 equiv of H₃PO₄, HCl or H₂SO₄, the yields and selectivities of 1a were 42% and 44%, 61% and 81%, and 77% and 82%, respectively. In the absence of *p*TsOH or any other acids (Table 1, entry 1a), the selectivity and yield of 1a were poor and the reaction was accompanied by products of di and triiodination at positions 2,4 and 2,4,6, respectively. For other ortho and para-substituted phenols, iodination without the promoting acid also afforded diiodinated by-products in low to moderate yields. The promotingeffect of pTsOH on the selectivity of iodination, as demonstrated by the change in sequence of pTsOH addition to the acetonitrile-substrate solution (adding last after NIS), showed that all, except for the iodination of 6, gave poor yields of the desired products, 1a-11a (Table 1, entries 1c-11c). We speculate that the role of pTsOH in the reaction is to suppress the formation of the phenolate anion and as a result, diminish iodination via the phenolic anion.

The most effective amount of *p*TsOH to promote optimum yield and regioselectivity was found to be 1 equiv. At 0.05 equiv of *p*TsOH, the yield and selectivity of **1a** were 69% and 89%, respectively. Increasing the amount of *p*TsOH to 0.1, 0.3 and 0.5 equiv did not improve the yields and selectivities of **1a**, which remained at 70% and 87–89%, respectively.

The best solvent for effecting regioselective iodination of phenols and analogues was acetonitrile, as was also shown in the





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Table 1

Effects of *p*-toluenesulfonic acid, solvents and temperature on the monoiodination of phenol and analogues^a

R = 11, 2.5 Call, 5, $T = 0.11, 2$ Coll, 2 Coll, 2 Coll, 4 Coll, 2
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Entry	Substrate	Solvent				Product co	Product	Isolated yield (%)				
			S.M.	2	4	6	2,4	2,6	4,6	2,4,6		
1a 1b 1c 1d 1e 1f 1g 1h 1i 1k	OH 1	CH ₃ CN ^b CH ₃ CN ^a CH ₃ CN ^c CH ₃ CN ^{a,d} CH ₃ CN ^{a,e} CH ₃ OH EtOAc THF 1,4-Dioxane CHCl ₃	29 0 30 8 11 2 99 2 20 0	3 4 3 6 5 17 0 16 22 13	26 95 33 86 84 77 1 78 58 86	- - - - - - - -	20 1 21 0 2 0 2 Trace 1	0 0 0 2 0 2 Trace 0	- - - - - - - - - - -	22 0 13 0 0 0 0 0 0 0 0	OH I Ia ⁸	95 81
2a 2b 2c	HO2	CH₃CN ^b CH₃CNª CH₃CN ^c	81 5 77	17 95 20	- - -		 -	2 0 3		 _	HO CH ₃ 2a ⁹	85
3a 3b 3c	HO CH ₃ 3	CH₃CN ^b CH₃CNª CH₃CN ^c	69 0 30	- - -	6 91 46	18 Trace 11	- - -	_ _ _	7 8 13	 -	HO CH ₃ 3a ¹⁰	89
4a 4b 4c	HO CH ₃ O 4	CH₃CN ^b CH₃CNª CH₃CN ^c	100 7 100	- - -	0 87 0	0 6 0	_ _ _		0 0 0	_ _ _	HO CH ₃ O I 4a ¹¹	66
5a 5b 5c	HO 5	CH₃CN ^b CH₃CN ^a CH₃CN ^c	84 2 4	- - -	10 95 92	6 3 4	- - -	_ _ _	0 0 0	 	HO I I I I I	88
6a 6b 6c	HO G	CH₃CN ^b CH₃CNª CH₃CN ^c	99 23 17	- -	<1 75 80	0 2 3	- - -	- - -	0 0 0	- - -	HO I HO I HO I HO I	73 72
7a 7b 7c 7d	HO CI 7	CH ₃ CN ^b CH ₃ CN ^a CH ₃ CN ^c CHCl ₃ ^a	36 14 27 6	- - -	16 82 23 76	4 4 8 18	 	 	44 0 42 0	 	HO CI CI CI	78 72
7e	HO CI	CH ₃ CN ^a	0	-	7	0	_	_	19 ^f	74 ^g	HO Br 7b ¹⁵	54
8a 8b 8c 8d	HO CI	CH ₃ CN ^b CH ₃ CN ^a CH ₃ CN ^c CHCl ₃ ^a	66 9 10 10	30 74 78 83	 	_ _ _ _	- - - -	4 17 12 7	 	- - - -	HO I Cl 8a ¹⁶	51 66

(continued on next page)

Table 1 (continued)

Entry	Substrate			Pro	duct co	mpositio	Product	Isolated yield (%)				
			S.M.	2	4	6	2,4	2,6	4,6	2,4,6		
9a 9b 9c	HO Br 9	CH₃CN ^b CH₃CN ^a CH₃CN ^c	45 2 15	 _	18 94 65	4 4 9	 _	 _	33 0 11	- - -	HO Br 1 9a ¹⁷	81
10a 10b 10c	OH 10	CH₃CN ^b CH₃CN ^a CH₃CN ^c	17 1 1	83 99 99	 _	- - -	 _	 _	 	- - -	OH 10a ¹⁸	93
11a 11b 11c	0H 11	CH₃CN ^b CH₃CNª CH₃CN ^c	100 16 95	0 3 2	0 81 3		0 0 0	- - -	- - -	- - -	OH 11a ¹⁹	78

^a Reaction conditions: *p*TsOH (0.5 mmol) was added to a stirred solution (solvent = 10 ml) containing the substrate (0.5 mmol) at room temperature or 0 °C. After 5 min, 1 equiv of NIS was added and the mixture was stirred for 14 h. The reaction was monitored by GC/MS until completion and the product composition was determined by GC/ MS. The major products were isolated by silica gel column chromatography (10–20% CH₂Cl₂/hexanes) and characterised by GC/MS, ¹H and ¹³C NMR. The numbers in the product composition denote the positions of iodination relative to the OH (numbered 1) of the phenol and S.M. refers to the substrate.

^b Without *p*TsOH.

^c pTsOH (1 equiv) was added to the stirred solution (solvent = 10 ml) containing the substrate and NIS after a 15-min delay.

^d The reaction mixture was stirred at room temperature for 8 h.

^e Reaction mixture was stirred at 0 °C for 8 h.

^f 2,4-Dibromo-6-chlorophenol (12%) and 4,6-diiodo-2-chlorophenol (7%) were obtained.

^g Compound **7b**.

syntheses of 3-halo and 3-halo-5-iodo analogues of N-acetyl-Ltyrsoine.^{6f} In acetonitrile, monoiodination of 1 at room temperature afforded 1a in 95% yield and selectivity (Table 1, entry 1b). In methanol, the yield and the selectivity of 1a were 77% and 79%, respectively (Table 1, entry 1f). On the other hand, there was no significant reaction in EtOAc (Table 1, entry 1g). In THF and 1,4-dioxane, iodination of 1 gave moderate yields and selectivities of 1a (Table 1, entries 1h and 1i). Chloroform was found to be an effective solvent for regioselective iodination, even though the yield of ortho iodination (13%) in CHCl₃ was higher compared to that obtained in acetonitrile (Table 1, entry 1k). However, chloroform proved to be a useful alternative solvent for the iodination of 8 to afford 8a in 83% yield, while the same reaction in acetonitrile gave only a 74% yield. This enhancement was not observed with 2-chloro and 2-bromophenol (7 and 9). Acetonitrile gave the highest yields of 7a and 9a. Nevertheless, chloroform is an alternative solvent for clean regioselective iodination in some cases (Table 1, entries 1k and 8d).

Lowering the temperature to 0 °C did not have a significant impact on the regioselectivity of phenol iodination. The selectivity of **1a** was 94% (Table 1, entry **1e**) after 8 h at 0 °C, while the selectivity of **1a** after 8 h at room temperature was 93% (Table 1, entry **1d**). Thus, subsequent monoiodinations of other substrates (compounds **2-11**) were conducted at room temperature using 1 equiv each of *p*TsOH and NIS. Iodination of *ortho*-substituted phenols occurred almost exclusively at the *para* position (relative to the OH). For all cases, except for **3**, which showed an amount of less than 1% for iodination occurred almost exclusively. For the *para*-substituted phenols, monoiodination occurred almost exclusively. For both *para* and *ortho*-substituted phenols, including substrate **1** also, monoiodination was the norm.

A preliminary study of bromination using pTsOH and N-bromosuccinimide (NBS) showed that bromination of phenol occurred almost exclusively at the *para* position with a yield of 92%. The versatility of the iodination methodology is further demonstrated in the one-pot synthesis of 2-bromo-6-chloro-4-iodophenol (**7b**) via iodination and bromination. First, using 1.15 equiv of NIS (14 h) followed by 1.2 equiv of NBS (4 h) at room temperature, **7** was converted into **7b** in 74% yield (Table 1, entry **7e**).¹⁵ Studies are underway to further explore the application of this methodology to monobromination and the one-pot sequential mixed halogenations of phenol analogues, and the results will be reported in due course.

Acknowledgements

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 Compound **1a**: mp 93 °C (lit.^{7a} mp 93–94 °C); ¹H NMR (300 MHz, CDCl₃): *δ* 5.10
- Compound 1a: mp 93 °C (lit.^{7a} mp 93–94 °C); ¹H NMR (300 MHz, CDCl₃): δ 5.10 (br s, 1H, OH), 6.62 (d, *J* = 9 Hz, 2H), 7.51 (d, *J* = 9 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃): δ 82.8, 117.8, 138.4, 155.2; GC/MS (EI) m/z (rel int.): 220 (100, M⁺), 191 (2, (M-CHO)⁺), 127 (4, I), 110 (4), 93 (26, (M-I)⁺), 74 (2), 65 (23), 53 (3), 39 (10).
 Compound 2a: colourless oil (lit.^{7b} light-brown oil); ¹H NMR (300 MHz, CDCl₃):
- Compound 2a: colourless oil (lit.^{7b} light-brown oil); ¹H NMR (300 MHz, CDCl₃): δ 2.24 (s, 3H), 5.17 (br s, 1H, OH), 6.87 (d, *J* = 8 Hz, 1H), 7.03 (d, *J* = 8 Hz, 1H), 7.47 (s, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 19.9, 85.4, 114.7, 130.9, 131.9, 138.3, 152.6; GC/MS (EI) *m/z* (rel int.): 234 (100, M⁺), 127 (4, I), 107 (33, (M-I)⁺), 77 (28), 63 (3), 51 (9), 39 (3).
- Compound **3a**: mp 65-67 °C (lit.^{7c} mp 66.5-68 °C); ¹H NMR (300 MHz, CDCl₃): δ 2.20 (s, 3H), 4.79 (br s, 1H, OH), 6.54 (d, *J* = 8 Hz, 1H), 7.35 (dd, *J* = 2 and 8 Hz, 1H), 7.43 (d, *J* = 2 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 15.4, 82.6, 117.1, 126.7, 135.8, 139.5, 153.7; GC/MS (EI) *m/z* (rel int.): 234 (100, M⁺), 127 (4, I), 107 (20, (M−I)⁺), 77 (34), 63 (4), 51 (7), 39 (4).
 Compound **4a**: colourless oil (lit.^{7d} mp 43 °C); ¹H NMR (300 MHz, CDCl₃): δ 3.87
- Compound 4a: colourless oil (lit.^{7d} mp 43 °C); ¹H NMR (300 MHz, CDCl₃): δ 3.87 (s, 3H), 5.59 (s, 1H, OH), 6.68 (d, *J* = 8 Hz, 1H), 7.18 (dd, *J* = 2 and 8 Hz, 1H), 7.22 (d, *J* = 2 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 56.2, 80.9, 116.5, 119.7, 130.4, 145.7, 147.4; GC/MS (EI) *m/z* (rel int.): 251 (8, (M+1)*), 250 (100, M*), 236 (3, ((M+1)-CH₃)*), 235 (45, (M-CH₃)*), 208 (1, ((M+1)-CH₃-CO)*), 207 (20, (M-CH₃-CO)*), 123 (4, (M–1)*), 108 (7, (M–1-CH₃)*), 94 (2), 80 (5), 79 (5), 63 (5), 52 (11).
- Compound 5a: mp 90 °C (lit.^{7e} mp 91–92 °C); ¹H NMR (300 MHz, CDCl₃): δ 2.64 (s, 3H), 6.78 (d, *J* = 9 Hz, 1H), 7.71 (dd, *J* = 2 and 9 Hz, 1H), 8.00 (d, *J* = 2 Hz, 1H), 12.18 (s, 1H, OH); ¹³C NMR (75 MHz, CDCl₃): δ 26.7, 79.7, 120.9, 139.2, 144.7, 152.7, 161.9, 203.5; GC/MS (EI) m/z (rel int.): 262 (100, M*), 247 (77, (M-CH₃)*), 219 (14, (M-COCH₃)*), 119 (4), 135 (3, (M–I)*), 127 (3, 1), 120 (7), 107 (3), 92 (12), 77 (5), 63 (12), 43 (12).

- Compound Ga: mp 62–63 °C (lit.^{7f} mp 78 °C); ¹H NMR (300 MHz, CDCl₃): δ 3.96 (s, 3H), 6.77 (d, *J* = 9 Hz, 1H), 7.69 (dd, *J* = 2 and 9 Hz, 1H), 8.13 (d, *J* = 2 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 52.6, 80.1, 114.5, 120.0, 138.3, 144.1, 161.2, 169.4; GC/MS (EI) *m/z* (rel int.): 279 (7, (M+1)⁺), 278 (85, M⁺), 247 (17, ((M+1)-CH₃O-H)⁺), 246 (100, (M-CH₃O-H)⁺), 219 (6), 218 (32), 191 (3), 190 (4), 151 (3, (M-L)⁺), 127 (3, 1), 120 (3), 119 (3), 92 (8), 91 (9), 63 (22), 53 (8), 38 (2).
 Compound **7a**: mp 53–54 °C (lit.^{7g} mp 54 °C); ¹H NMR (300 MHz, CDCl₃): δ 5.57
- Compound **7a**: mp 53-54 °C (lit.^{7k} mp 54 °C); ¹H NMR (300 MHz, CDCl₃): δ 5.57 (br s, 1H, OH), 6.78 (d, *J* = 9 Hz, 1H), 7.46 (dd, *J* = 2 and 9 Hz, 1H), 7.62 (d, *J* = 2 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 81.5, 118.2, 125.0, 136.9, 137.3, 151.4; GC/MS (El) *m/z* (rel int.): 256 (32, (M+2)⁴), 254 (100, M⁴), 129 (8, ((M+2)-1)⁴), 127 (34, (M-1)⁴), 99 (21), 91 (10), 73 (8), 63 (21).
 Compound **7b**: mp 82-84 °C (lit.^{7h} mp 81-82 °C); ¹H NMR (300 MHz, CDCl₃): δ
- Compound **7b**: mp 82–84 °C (lit.^{7h} mp 81–82 °C); ¹H NMR (300 MHz, CDCl₃): δ
 5.99 (s, 1H, OH), 7.46 (d, *J* = 2 Hz, 1H), 7.74 (d, *J* = 2 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 83.9, 112.9, 119.7, 132.0, 139.6, 150.4; GC/MS (EI) *m/z* (rel int.): 336 (26, (M+4)*), 334 (100, (M+2)*), 332 (78, M*), 305 (1, ((M+2)-CHO)*), 303 (1, (M-CHO)*), 209 (1, ((M+4)-I)*), 207 (3, ((M+2)-I)*), 205 (2, (M–I)*), 181 (6), 179 (26), 177 (19), 143 (6), 141 (7), 127 (9, I), 97 (13, (M-Br–I–CHO)*), 62 (20, (M-Br–CI–I–CHO)*), 53 (5).
- Compound 8a: mp 75-76 °C (lit.⁷¹ mp 75-77 °C); ¹H NMR (300 MHz, CDCl₃): δ
 5.34 (s, 1H, OH), 6.91 (d, J = 9 Hz, 1H), 7.21 (dd, J = 2 and 9 Hz, 1H), 7.63(d, J = 2 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 85.4, 115.7, 126.1, 130.1, 137.2, 153.8; GC/MS (El) m/z (rel int.): 256 (33, (M+2)⁺), 254 (100, M⁺), 225 (1, (M-CHO)⁺), 129 (4, ((M+2)-I)⁺), 127 (19, (M-I)⁺), 101 (7), 99 (23), 73 (7), 63 (15), 53 (4).
- (4, ((M+2)-I)⁺), 127 (19, (M−I)⁺), 101 (7), 99 (23), 73 (7), 63 (15), 53 (4).
 17. Compound 9a: mp 49–50 °C (lit.^{7h} mp 51 °C); ¹H NMR (300 MHz, CDCl₃): δ 5.49 (s, 1H, OH), 6.71 (d, *J* = 9 Hz, 1H), 7.41 (dd, *J* = 2 and 9 Hz, 1H), 7.67 (d, *J* = 2 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 81.0, 110.3, 117.1, 137.0, 138.6, 151.3; GC/MS (EI) *m/z* (rel int.): 300 (98, (M+2)⁺), 298 (100, M⁺), 271 (1, ((M+2)-CHO)⁺), 269 (1, (M-CHO)⁺), 173 (16, ((M+2)-I)⁺), 171 (17, (M−I)⁺), 145 (11), 143 (12), 127 (7, I), 119 (3), 117 (3), 92 (19), 74 (3), 63 (28), 53 (8), 38 (3).
 18. Compound 10a: mp 92–93 °C (lit.^{7j} mp 91–92 °C); ¹H NMR (300 MHz, CDCl₃): δ
- Compound **10a**: mp 92–93 °C (lit.^{7j} mp 91–92 °C); ¹H NMR (300 MHz, CDCl₃): δ 7.25 (d, J = 8 Hz, 1H), 7.38 (t, J = 8 Hz, 1H), 7.55 (t, J = 8 Hz, 1H), 7.74 (d, J = 8 Hz, 2H), 7.93 (d, J = 8 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 86.2, 116.4, 124.2, 128.2, 128.3, 129.7, 130.3, 130.6, 134.8, 153.8; GC/MS (EI) *m/z* (rel int.): 270 (100, M⁺), 241 (2, (M-CHO)⁺), 143 (9, (M–I)⁺), 127 (2, I), 115 (36), 89 (4), 74 (2), 63 (5) 39 (1).
- 0. Corpound **11a**: mp 78 °C (dec) (lit.^{20a} mp 104–105 °C; lit.^{20b} mp 104 °C); ¹H NMR (300 MHz, CDCl₃): δ 5.48 (br s, 1H, OH), 6.64 (d, *J* = 8 Hz, 1H), 7.55 (dt, *J* = 2 and 8 Hz, 1H), 7.62 (dt, *J* = 2 and 8 Hz, 1H), 7.89 (d, *J* = 8 Hz, 1H), 8.06 (dd, *J* = 1 and 8 Hz, 1H), 8.19 (dd, *J* = 1 and 8 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃): δ 88.2, 108.2, 110.1, 122.3, 126.1, 128.3, 131.9, 135.1, 136.8, 152.4; GC/MS (EI) *m*/ *z* (rel int.): 270 (100, M⁺), 241 (3, (M-CHO)⁺), 207 (1), 144 (10, ((M+1)-I)⁺), 143 (11, (M−I)⁺), 135 (5), 127 (3, 1), 115 (52), 89 (7), 63 (7), 32 (5).
- (a) Sket, B.; Zupet, P.; Zupan, M. J. Chem. Soc., Perkin Trans. 1 1989, 2279–2281;
 (b) Sumi Mitra, S.; Sreekumar, K. React. Funct. Polym. 1997, 32, 281–291. At this stage we are unable to explain the discrepancy between our melting point and the literature melting points. The ¹H NMR and MS data of 11a matched those reported in the literature.