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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.

Iodination of phenols furnishes important synthetic intermediates[1] 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 $NaClO_2$–NaI–HCl,[4a] ICl,[4b] I_2-tetrabutylammonium peroxydisulfate,[4c] bis(*sym*-collidine)iodine(I) hexafluorophosphate,[4d] benzyltrimethylammonium dichloroiodate,[4e] chloramine T-NaI[4f] and NaI-*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-I_2[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-2-chloro-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 CF_3SO_3H (as solvent for deactivated systems),[6a] catalytic hydroxy(tosyloxy)iodobenzene (HTIB),[6b] catalytic *p*-toluenesulfonic acid (*p*TsOH),[6c] CH_3CN (as solvent for the activated systems)[6d] and catalytic CF_3CO_2H.[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 *p*TsOH were also investigated for their promoting effect on the selectivity of *para*-iodination of phenol. With 1 equiv of CH_3CO_2H, the yield and selectivity of **1a** were 14% and 16%, respectively. With 1 equiv of H_3PO_4, HCl or H_2SO_4, 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 promoting-effect of *p*TsOH on the selectivity of iodination, as demonstrated by the change in sequence of *p*TsOH 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 *p*TsOH 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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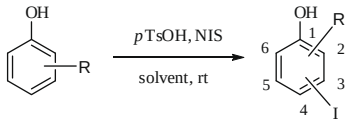
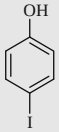
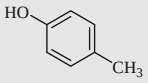
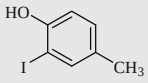
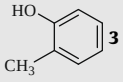
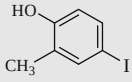
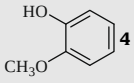
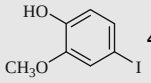
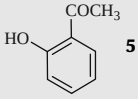
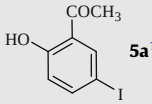
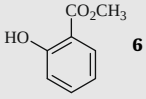
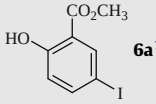
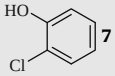
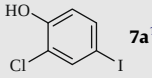
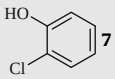
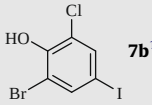
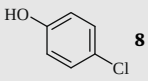
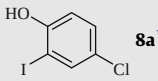
Table 1
Effects of *p*-toluenesulfonic acid, solvents and temperature on the monoiodination of phenol and analogues[a]

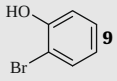
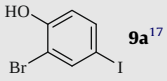
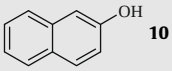
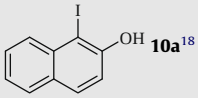
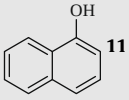
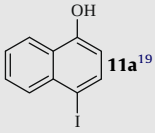


R = H, 2,3-C_4H_4, 3,4-C_4H_4, 2-OCH_3, 2-Br, 2-Cl, 4-Cl, 2-CH_3, 4-CH_3, 2-$COCH_3$, 2-CO_2CH_3

Entry	Substrate	Solvent	Product composition[a] (%)								Product	Isolated yield (%)
			S.M.	2	4	6	2,4	2,6	4,6	2,4,6		
1a	 **1**	CH_3CN[b]	29	3	26	—	20	0	—	22	 **1a**[8]	
1b		CH_3CN[a]	0	4	**95**	—	1	0	—	0		95
1c		CH_3CN[c]	30	3	33	—	21	0	—	13		
1d		CH_3CN[a,d]	8	6	86	—	0	0	—	0		
1e		CH_3CN[a,e]	11	5	84	—	0	0	—	0		
1f		CH_3OH	2	17	77	—	2	2	—	0		
1g		EtOAc	99	0	1	—	0	0	—	0		
1h		THF	2	16	78	—	2	2	—	0		
1i		1,4-Dioxane	20	22	58	—	Trace	Trace	—	0		
1k		$CHCl_3$	0	13	**86**	—	1	0	—	0		81
2a	 **2**	CH_3CN[b]	81	17	—	—	—	2	—	—	 **2a**[9]	85
2b		CH_3CN[a]	5	**95**	—	—	—	0	—	—		
2c		CH_3CN[c]	77	20	—	—	—	3	—	—		
3a	 **3**	CH_3CN[b]	69	—	6	18	—	—	7	—	 **3a**[10]	89
3b		CH_3CN[a]	0	—	**91**	Trace	—	—	8	—		
3c		CH_3CN[c]	30	—	46	11	—	—	13	—		
4a	 **4**	CH_3CN[b]	100	—	0	0	—	—	0	—	 **4a**[11]	66
4b		CH_3CN[a]	7	—	**87**	6	—	—	0	—		
4c		CH_3CN[c]	100	—	0	0	—	—	0	—		
5a	 **5**	CH_3CN[b]	84	—	10	6	—	—	0	—	 **5a**[12]	88
5b		CH_3CN[a]	2	—	**95**	3	—	—	0	—		
5c		CH_3CN[c]	4	—	92	4	—	—	0	—		
6a	 **6**	CH_3CN[b]	99	—	<1	0	—	—	0	—	 **6a**[13]	73
6b		CH_3CN[a]	23	—	**75**	2	—	—	0	—		
6c		CH_3CN[c]	17	—	**80**	3	—	—	0	—		72
7a	 **7**	CH_3CN[b]	36	—	16	4	—	—	44	—	 **7a**[14]	78
7b		CH_3CN[a]	14	—	**82**	4	—	—	0	—		
7c		CH_3CN[c]	27	—	23	8	—	—	42	—		
7d		$CHCl_3$[a]	6	—	**76**	18	—	—	0	—		72
7e	 **7**	CH_3CN[a]	0	—	7	0	—	—	19[f]	**74**[g]	 **7b**[15]	54
8a	 **8**	CH_3CN[b]	66	30	—	—	—	4	—	—	 **8a**[16]	51
8b		CH_3CN[a]	9	**74**	—	—	—	17	—	—		
8c		CH_3CN[c]	10	78	—	—	—	12	—	—		
8d		$CHCl_3$[a]	10	**83**	—	—	—	7	—	—		66

(*continued on next page*)

Table 1 (*continued*)

Entry	Substrate	Solvent	Product composition[a] (%)								Product	Isolated yield (%)
			S.M.	2	4	6	2,4	2,6	4,6	2,4,6		
9a	 **9**	CH_3CN[b]	45	—	18	4	—	—	33	—	 **9a**[17]	81
9b		CH_3CN[a]	2	—	**94**	4	—	—	0	—		
9c		CH_3CN[c]	15	—	65	9	—	—	11	—		
10a	 **10**	CH_3CN[b]	17	83	—	—	—	—	—	—	 **10a**[18]	93
10b		CH_3CN[a]	1	**99**	—	—	—	—	—	—		
10c		CH_3CN[c]	1	99	—	—	—	—	—	—		
11a	 **11**	CH_3CN[b]	100	0	0	—	0	—	—	—	 **11a**[19]	78
11b		CH_3CN[a]	16	3	**81**	—	0	—	—	—		
11c		CH_3CN[c]	95	2	3	—	0	—	—	—		

[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% CH_2Cl_2/hexanes) and characterised by GC/MS, ^1H and ^{13}C 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] *p*TsOH (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-L-tyrsoine.[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 $CHCl_3$ 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 at position 6, iodinations at position 6 of other substrates were no higher than 4%. 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 *p*TsOH 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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References and notes

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8. *Compound* **1a**: mp 93 °C (lit.[7a] mp 93–94 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.10 (br s, 1H, OH), 6.62 (d, J = 9 Hz, 2H), 7.51 (d, J = 9 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 82.8, 117.8, 138.4, 155.2; GC/MS (EI) *m/z* (rel int.): 220 (100, M^+), 191 (2, $(M\text{-}CHO)^+$), 127 (4, I), 110 (4), 93 (26, $(M-I)^+$), 74 (2), 65 (23), 53 (3), 39 (10).
9. *Compound* **2a**: colourless oil (lit.[7b] light-brown oil); ^{1}H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): 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).
10. *Compound* **3a**: mp 65–67 °C (lit.[7c] mp 66.5–68 °C); ^{1}H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): 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).
11. *Compound* **4a**: colourless oil (lit.[7d] mp 43 °C); ^{1}H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): 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, $((M+1)\text{–}CH_3)^+$), 235 (45, $(M\text{-}CH_3)^+$), 208 (1, $((M+1)\text{-}CH_3\text{–}CO)^+$), 207 (20, $(M\text{-}CH_3\text{–}CO)^+$), 123 (4, $(M-I)^+$), 108 (7, $(M-I\text{ -}CH_3)^+$), 94 (2), 80 (5), 79 (5), 63 (5), 52 (11).
12. *Compound* **5a**: mp 90 °C (lit.[7e] mp 91–92 °C); ^{1}H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): 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, $(M\text{-}CH_3)^+$), 219 (14, $(M\text{-}COCH_3)^+$), 191 (4), 135 (3, $(M-I)^+$), 127 (3, I), 120 (7), 107 (3), 92 (12), 77 (5), 63 (12), 43 (12).
13. *Compound* **6a**: mp 62–63 °C (lit.[7f] mp 78 °C); ^{1}H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): 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, $((M+1)\text{–}CH_3O\text{–}H)^+$), 246 (100, $(M\text{-}CH_3O\text{–}H)^+$), 219 (6), 218 (32), 191 (3), 190 (4), 151 (3, $(M-I)^+$), 127 (3, I), 120 (3), 119 (3), 92 (8), 91 (9), 63 (22), 53 (8), 38 (2).
14. *Compound* **7a**: mp 53–54 °C (lit.[7g] mp 54 °C); ^{1}H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): δ 81.5, 118.2, 125.0, 136.9, 137.3, 151.4; GC/MS (EI) *m/z* (rel int.): 256 (32, $(M+2)^+$), 254 (100, M^+), 129 (8, $((M+2)\text{-}I)^+$), 127 (34, $(M-I)^+$), 99 (21), 91 (10), 73 (8), 63 (21).
15. *Compound* **7b**: mp 82–84 °C (lit.[7h] mp 81–82 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.99 (s, 1H, OH), 7.46 (d, J = 2 Hz, 1H), 7.74 (d, J = 2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): 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, $((M+2)\text{-}CHO)^+$), 303 (1, $(M\text{-}CHO)^+$), 209 (1, $((M+4)\text{-}I)^+$), 207 (3, $((M+2)\text{-}I)^+$), 205 (2, $(M-I)^+$), 181 (6), 179 (26), 177 (19), 143 (6), 141 (7), 127 (9, I), 97 (13, $(M\text{-}Br\text{–}I\text{–}CHO)^+$), 62 (20, $(M\text{-}Br\text{–}Cl\text{–}I\text{–}CHO)^+$), 53 (5).
16. *Compound* **8a**: mp 75–76 °C (lit.[7i] mp 75–77 °C); ^{1}H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): δ 85.4, 115.7, 126.1, 130.1, 137.2, 153.8; GC/MS (EI) *m/z* (rel int.): 256 (33, $(M+2)^+$), 254 (100, M^+), 225 (1, $(M\text{-}CHO)^+$), 129 (4, $((M+2)\text{-}I)^+$), 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); ^{1}H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): 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, $((M+2)\text{-}CHO)^+$), 269 (1, $(M\text{-}CHO)^+$), 173 (16, $((M+2)\text{-}I)^+$), 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); ^{1}H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): 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, $(M\text{-}CHO)^+$), 143 (9, $(M-I)^+$), 127 (2, I), 115 (36), 89 (4), 74 (2), 63 (5) 39 (1).
19. *Compound* **11a**: mp 78 °C (dec) (lit.[20a] mp 104–105 °C; lit.[20b] mp 104 °C); ^{1}H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (75 MHz, $CDCl_3$): 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, $(M\text{-}CHO)^+$), 207 (1), 144 (10, $((M+1)\text{-}I)^+$), 143 (11, $(M-I)^+$), 135 (5), 127 (3, I), 115 (52), 89 (7), 63 (7), 32 (5).
20. (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 ^{1}H NMR and MS data of **11a** matched those reported in the literature.