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On the *para*-selective chlorination of *ortho*-cresol

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Abstract—Merrifield-bound *o*-cresol undergoes electrophilic aromatic chlorination using SO_2Cl_2 leading to *para*/*ortho* ratios in excess of 50, the highest such ratio reported for this chlorinating agent. Model studies suggest that this significant *para*/*ortho* ratio results not just from steric effects but that considerable electronic influence can be detected.

1. Introduction

Commercial applications of isomerically pure *ortho*- and *para*-chlorophenols[1] include dyestuffs, preservatives, disinfectants, insecticides and herbicides. 4-Chloro-2-methylphenol (*para*-chlorocresol; PCC), for example, is commercially important in the manufacture of 4-chloro-2-methyl-phenoxyacetic acid, a major phenoxy herbicide used to control weeds in small grains[2] and for post-emergence control of many broad-leaved weeds in cereals, grassland, and asparagus.[3] In addition, PCC is used also to make 4-chloro-2-methylphenoxybutyric acid for selective post-emergence weed control in leguminous crops (e.g. peas and clover) and in under-sown cereals where the analogous phenoxyacetic acid derivatives would damage the legumes.[4]

Chloro-substitution in 2-, 4- or 2,4-positions greatly enhances the herbicidal activity of phenols.[4] Consequently, considerable efforts have been directed towards controlling *para*-(4-position) selectivity in the chlorination of *o*-cresol over *ortho*-(6-position) and poly-chlorination [$R_{p/o}$=*para*/*ortho* ratio; Scheme 1(a)].

Phenol halogenation is usually so fast that it can be carried out in dilute aqueous solutions at room temperature.[5] However, since Cl_2 is such a strong halogenating agent that polychlorination occurs frequently, the search for milder chlorinating agents has turned to main-group derivatives such as chlorodimethylsulfonium chloride ($Me_2SCl^+Cl^-$),[5] *N*-chloroamines and ammonium salts[6] and sulfuryl chloride (SO_2Cl_2),[7] among several others.[8] Indeed, *N*-chloroamines have proved extremely selective *para*-chlorinating agents for *o*-cresol in acid solvent (trifluoroacetic or aqueous sulfuric acids),[6] returning high $R_{p/o}$ values <65. However, for the commercially favoured reagent SO_2Cl_2, $R_{p/o}$ have generally been <10 unless Lewis basic[8] (ethers, organonitrogen compounds, organosulfur compounds) or Lewis acidic[9] (metal halides) species are added; raising $R_{p/o}$ values for *o*-cresol to ca. 20.[10]

It has been reported that *para*-chlorination is favoured over *ortho*-chlorination as the steric demand of the chlorinating agent increases.[10] Consequently, substituting a cresol ether (ROC_6H_4-2-CH_3) for *o*-cresol (HOC_6H_4-2-CH_3) should also provide increased steric protection *ortho* to the phenoxy function. Revealingly, it has been found that anisole is chlorinated with greater regioselectivity than parent phenol by chloroamine salts.[6] Moreover, we reasoned that significant advantages might accrue from attachment of the cresol substrate to a polymer resin via an ether linkage including, (i) simplified synthetic chemistry, (ii) potentially greater steric protection of the *ortho* site by secondary or tertiary polymer structure and (iii) potential for parallel processing, for example, in the screening of different chlorination agents and additives. Consequently, we decided to work with *o*-cresol bound to Merrifield resin.

2. Results and discussion

2.1. Chlorination of 4-substituted benzyl-*o*-cresol ethers

However, we first wished to ascertain if our strategy had potential. We therefore prepared benzylphenol ether $PhCH_2OC_6H_4$-2-CH_3,[11] performed chlorination and subsequent debenzylation as outlined in Scheme 1(b) to afford a *para*/*ortho* ratio $R_{p/o}$ of 40,[12] considerably higher than previously reported ratios using SO_2Cl_2 as a chlorinating agent. Armed with this valuable model evidence we

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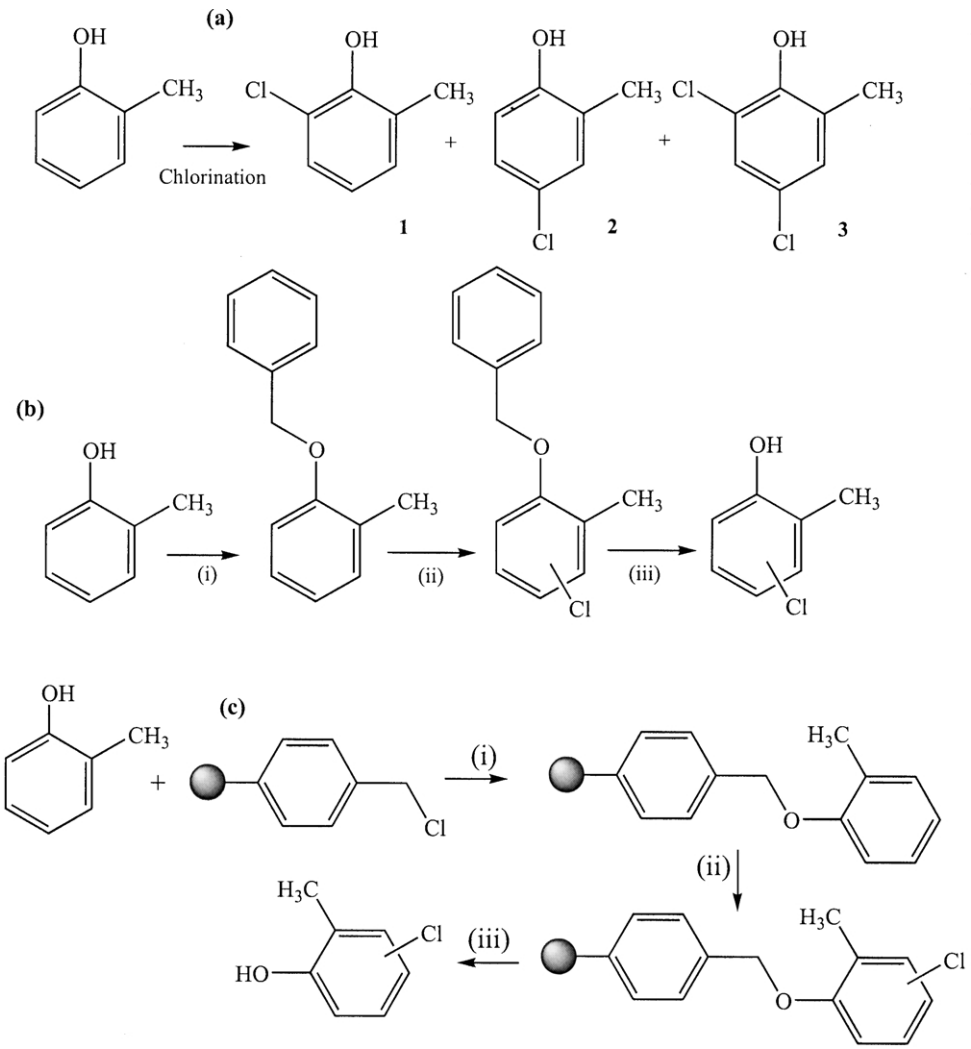


Scheme 1. (a) Chlorination of 2-methylphenol (*o*-cresol) resulting in 6-chloro-2-methylphenol, 4-chloro-2-methylphenol and 4,6-dichloro-2-methylphenol; (b) (i) BzCl, NaOH, 1 h, reflux; (ii) SO_2Cl_2, CH_2Cl_2, 2 h, 35°C; (iii) Me_3SiI (2 equiv.), CH_2Cl_2, 2 h, 25°C; (c) (i) Cs_2CO_3, NaI, DMF 48 h, 90%; (ii) SO_2Cl_2, CH_2Cl_2, 25°C, 2 h; (iii) TFA, CH_2Cl_2, 25°C.

performed the same chemical transformations on *o*-cresol bound to Merrifield resin (Scheme 1(c)).

2.2. Chlorination of Merrifield resin-linked *o*-cresol

The coupling step (i) proceeded smoothly following literature precedent.[13] Quantitative analysis of the coupling efficiency is not easily achieved. Both FT-IR and solid state ^{13}C NMR (see below) afford qualitative information but we have found that mass difference measurements are the best method for determining coupling efficiency, subsequently allowing us to determine an effective reaction time of 48 h whereupon ca. 85–87% of 1.0–1.6 mmol/g resin active sites have been replaced by *o*-cresol. This figure reaches 89% coupling efficiency after 72 h. Chlorination [step (ii)] proceeded smoothly also followed by decoupling [step (iii)] for which, in contrast to the model benzyl ether, we found trifluoroacetic acid in CH_2Cl_2 (1:1 v/v) to be very effective. Upon decoupling from the polymer resin, both product composition and $R_{p/o}$ ratio was determined by 500 MHz NMR to be consistently in excess of 50.[12]

Reproducibility of this result is an important issue since several factors, such as the coupling efficiency, the resin loading, the volume of swelling solvent (CH_2Cl_2) used and the number of equivalents of SO_2Cl_2 employed during the chlorination step, may influence the reaction, and hence $R_{p/o}$. The coupling step was examined on resins of different loading: (i) high loading 3.1 mmol Cl/g resin and (ii) low loading 1.0–1.6 mmol Cl/g resin under conditions of different reaction times (48 and 72 h), in presence of sodium iodide and caesium carbonate in DMF at room temperature. Mass difference measurements revealed that the high loading resin returned a coupling efficiency of 74–75% bound *o*-cresol after 48 h and 80% after 72 h, somewhat lower than those values for the low loading resin above. The $R_{p/o}$ ratio was measured following chlorination in the presence of different amounts of swelling solvent (CH_2Cl_2), at room temperature, over a reaction time of 2 h with differing quantities of chlorinating agent (SO_2Cl_2). Results revealed that $R_{p/o}$ tended to increase with a larger quantity of solvent (e.g. $R_{p/o}$ ca. 25 with 1 cm^3 CH_2Cl_2 and $R_{p/o}$ ca. 55 with 4 cm^3 CH_2Cl_2). A complete explanation has yet to be

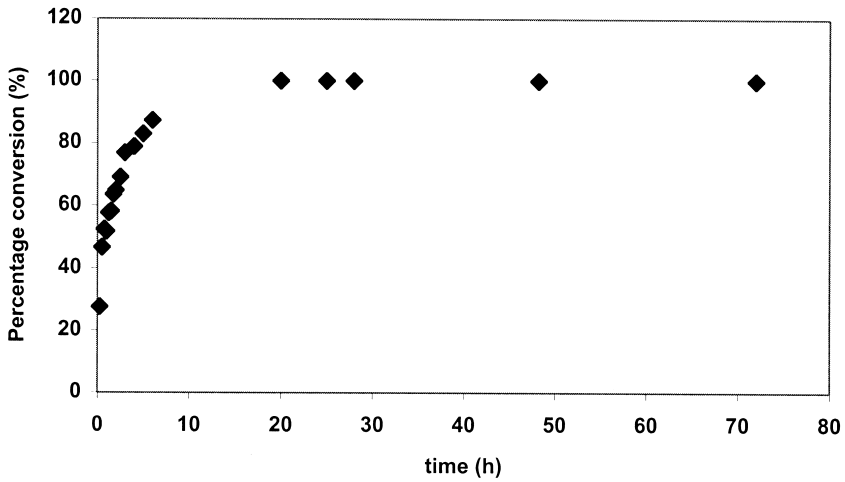


Figure 1. Percentage conversion (%) vs time (h) to chlorinated products in the reaction between *o*-cresol and SO_2Cl_2; CH_2Cl_2 solvent; 298 K.

provided but it seems clear that degree of dilution is an important feature.

Obviously, quantitative product analysis is most easily achieved after cleavage from the polymer resin. Nevertheless, qualitative analysis via solid-state $^{13}C\{^1H\}$ NMR is revealing. Cross polarisation magic angle spinning (CPMAS) analysis of Merrifield resin clearly differentiates aromatic from non-aromatic carbons.[14] Upon loading the resin with *o*-cresol $^{13}C\{^1H\}$ analysis clearly locates signals associated with the bound *o*-cresol methyl and phenolic *ipso* carbon. Similarly, loading Merrifield with pure 4-chloro- and 6-chloro-2-cresol reveals significant shifts in key aromatic resonances, mirroring similar shift changes in solution-phase spectra. CPMAS NMR analysis of a sample of *o*-cresol-bound Merrifield resin which has been chlorinated using the protocol outlined in Supplementary Information reveals only 4-chlorination.

2.3. Chlorination of 4-substituted benzyl-*o*-cresol ethers. Electronic or steric control?

To what extent are the $R_{p/o}$ ratios observed influenced by steric and/or electronic factors? Obviously, differential steric effects at the *ortho* and *para* sites in phenolic systems, ArO*H*, are likely to lead to favouring of the latter. Indeed, simple MM2 calculations (Chem3D PRO) of putative transition states for both *para* and *ortho*-chlorination in HOC_6H_4-2-CH_3 suggest an $R_{p/o}$ value of ca. 5 based on sterics alone.[†]

Consequently, we have examined $R_{p/o}$ values for a range of substituted benzylphenol ethers ($4'$-$XC_6H_4CH_2OC_6H_4$-2-CH_3; X=H, NO_2, CF_3, Cl, CH_3), to investigate any relationship between $R_{p/o}$ and electronic parameters of the substituents. In each case we have compared the results to our standard, chlorination of *o*-cresol using SO_2Cl_2 in CH_2Cl_2 solvent at the same temperature (298 K) and at the same concentration (0.57 mmol). In Fig. 1 is reproduced the percentage conversion (%) vs time (h) to chlorinated products in the reaction between *o*-cresol and SO_2Cl_2. Reaction has essentially reached completion after 20 h and during this time, the $R_{p/o}$ values vary between 4.0 and 5.9 but after 20 h start to level off at 3.5. There does not appear to be any regular variation in $R_{p/o}$ value during the reaction. For each system (X=H, NO_2, CF_3, Cl, CH_3) results reveal that reaction proceeds smoothly to afford only *para*-chloro,

Table 1. Reactions of SO_2Cl_2 with X–$C_6H_4CH_2OC_6H_4$-2-CH_3 (0.57 mmol) in CH_2Cl_2 solvent, 298 K

X	Conversion (%)	*p*-Chloro	*o*-Chloro	Dichloro	*o*-Cresol (%) (recovered)	$R_{p/o}$
H	94.5	92.3	1.3	0.9	5.5	71
Cl	90.6	88.8	0.9	0.9	9.4	98
NO_2	94.4	91.2	1.0	2.2	5.6	91
CF_3	90.4[a]	88.8	0.6	1.0	9.6	148
CH_3	97.8	96.6	0.8	0.4	2.2	120

[a] After 4 h.

[†] Chem3D calculations on putative transition states for the chlorination of benzyl-*o*-cresol ether (**C**) and (**D**) and parent *o*-cresol itself (**A** and **B**) are instructive. If we use the Hammond postulate to approximate the rate-determining transition state to model intermediates (**C**) and (**D**) we find a greater steric energy differential in the ether system over the parent phenol analogues (**A**) and (**B**). Under kinetically controlled conditions, the energy difference between (**A**) and (**B**) may be equated to the energy difference between rate-determining transition states. If rate constants leading to *para* and *ortho* products are k_p and k_o, respectively, one may suppose that $k_p/k_o = \exp(-\Delta\Delta E/RT)$ where $\Delta\Delta E$ is the energy difference between (**A** or **C**) and (**B** or **D**) (10.1 kJ mol^{-1}). Under these conditions k_p/k_o ca. 5 for **A/B**, very close to the values observed in practise; 3.5–6. Moreover, k_p/k_o ca. 59 for **C/D**, considerably larger than for **A/B** but comensurate with experimental values (vide supra).

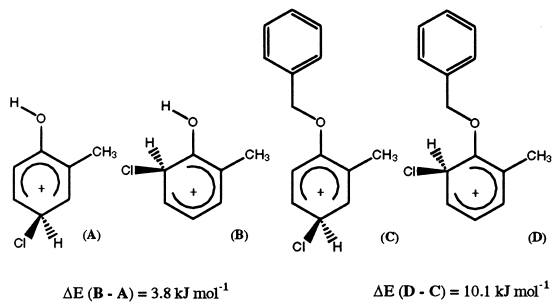


Table 2. Characterising data for benzyloxy-benzene derivatives

Compound name	Microanalysis (%) Found (required)	MS(EI) *m/z*	^{1}H; ^{13}C{^{1}H} NMR δ($CDCl_3$)
1-Benzyloxy-2-methyl-6-chlorobenzene	C 72.1(72.3); H 5.8(5.6); Cl 15.1(15.2)	232 (8%, $[C_{14}H_{13}OCl]^{+\cdot}$), 141 (8%, $[C_7H_6OCl]^+$), 91 (100%, $[C_7H_7]^+$), 77 (31%, $[C_6H_5]^+$), 65 (35%, $[C_5H_5]^+$), 51 (26%, $[C_4H_3]^+$), 39 (19%, $[C_3H_3]^+$)	^{1}H NMR δ($CDCl_3$): 2.27 (s, 3H, CH_3), 4.96 (s, 2H, H_d, H_e), 6.96 (dd, 1H, $^3J_{HbHc}$=$^3J_{HbHa}$=7.8 Hz, H_b), 7.08 (d, 1H, $^3J_{HbHc}$=7.8 Hz, H_c), 7.24 (d, 1H, $^3J_{HaHb}$=7.8 Hz, H_a), 7.35–7.52 (m, 5H, H_{f-j}); ^{13}C NMR δ($CDCl_3$): 16.6 (C_7), 74.4 (C_8), 124.7 (C_4), 128.1 (C_6), 128.2 (C_5), 128.2 (C_{11}, C_{13}), 128.5 (C_{10}, C_{14}, C_{12}), 129.6 (C_3), 133.7 (C_2), 137.1 (C_9), 153.1 (C_1)
1-(4-Methylbenzyloxy)-2-methylbenzene	C 84.9(84.9); H 7.4(7.6)	212 (19%, $[C_{15}H_{16}O]^+$), 105 (100%, $[C_8H_9]^+$), 91 (6%, $[C_7H_7]^+$), 77 (45%, $[C_6H_5]^+$), 65 (10%, $[C_5H_5]^+$), 51 (13%, $[C_4H_3]^+$), 39 (13%, $[C_3H_3]^+$)	^{1}H NMR δ($CDCl_3$): 2.27 (s, 3H, C^7H_3), 2.36 (s, 3H, $C^{15}H_3$), 5.04 (s, 2H, H_e, H_f), 6.85–6.89 (m, 2H, Ha, Hc), 7.12–7.16 (m, 2H, Hb, Hd), 7.19 (d, 2H, $^3J_{Hh,iHg,j}$=7.8 Hz, Hh, Hi), 7.33 (d, 2H, $^3J_{Hg,jHh,I}$=8.0 Hz, Hg, Hj); ^{13}C NMR δ($CDCl_3$): 16.4 (C_7), 21.2 (C_{15}), 69.8 (C_8), 111.5 (C_6), 120.5 (C_4), 126.7 (C_5), 127.2 (C_2, C_{10}, C_{14}), 129.2 (C_{11}, C_{13}), 130.7 (C_3), 134.7 (C_{12}), 137.3 (C_9), 159.7 (C_1)
1-(4-Methylbenzyloxy)-2-methyl-4-chlorobenzene	C 72.8(73.0); H 6.0(6.1); Cl 14.2(14.4)	246 (17.5%, $[C_{15}H_{15}OCl]^{+\cdot}$), 141 (10%, $[C_7H_7OCl]^+$), 105 (100%, $[C_8H_9]^+$), 77 (58%, $[C_6H_5]^+$), 51 (23%, $[C_4H_3]^+$)	^{1}H NMR δ($CDCl_3$): 2.23 (s, 3H, C^7H_3), 2.36 (s, 3H, $C^{15}H_3$), 5.01 (s, 2H, H_d, H_e), 6.78 (d, 1H, $^3J_{HaHb}$=8.6 Hz, H_a), 7.07 (d(d), 1H, $^3J_{HaHb}$=8.6 Hz, $^4J_{HbHc}$=2.6 Hz, H_b), 7.12 (d, 1H, $^4J_{HcHb}$=2.6 Hz, H_c), 7.19 (d, 2H, $^3J_{Hg,hHf,I}$=7.9 Hz, H_g, H_h), 7.30 (d, 2H, $^3J_{Hg,hHf,i}$=7.9 Hz, H_f, H_i); ^{13}C NMR δ($CDCl_3$): 16.3 (C_7), 21.2 (C_{15}), 70.2 (C_8), 112.6 (C_6), 125.2 (C_2), 126.3 (C_5), 127.3 (C_{10}, C_{14}), 129.1 (C_4), 129.3 (C_{11}, C_{13}), 130.5 (C_3), 134.0 (C_{12}), 137.7 (C_9), 155.6 (C_1)
1-(4-Methylbenzyloxy)-2-methyl-6-chlorobenzene	C 73.0(73.0); H 6.3(6.3); Cl 14.1(14.4)	246 (19%, $[C_{15}H_{15}OCl]^{+\cdot}$), 141 (9%, $[C_7H_7OCl]^+$), 105 (100%, $[C_8H_9]^+$), 91 (7%, $[C_7H_7]^+$), 77 (52%, $[C_6H_5]^+$), 65 (8%, $[C_5H_5]^+$), 51 (20%, $[C_4H_3]^+$), 39 (11%, $[C_3H_3]^+$)	^{1}H NMR δ($CDCl_3$): 2.26 (s, 3H, C^7H_3), 2.37 (s, 3H, $C^{15}H_3$), 4.92 (s, 2H, H_d, H_e), 6.96 (dd, 1H, $^3J_{HcHb}$=$^3J_{HaHb}$=7.7 Hz, H_b), 7.07 (d, 1H, $^3J_{HcHb}$=7.7 Hz, H_c), 7.20 (d, 2H, $^3J_{Hg,hHf,I}$=7.8 Hz, H_g, H_h), 7.24 (d, 1H, $^3J_{HaHb}$=7.7 Hz, H_a), 7.40 (d, 2H, $^3J_{Hg,hHf,I}$=7.8 Hz, H_f, H_i); ^{13}C NMR δ($CDCl_3$): 16.6 (C_7), 21.3 (C_{15}), 74.4 (C_8), 124.7 (C_4), 128.1 (C_5), 128.1 (C_6), 128.4 (C_{10}, C_{14}), 129.2 (C_{11}, C_{13}), 129.5 (C_3), 133.7 (C_2), 134.1 (C_{12}), 138.0 (C_9), 153.2 (C_1)
1-(4-Chlorobenzyloxy)-2-methyl-4-chlorobenzene	C 59.9(62.9); H 4.6(4.5)	266 (22%, $[C_{14}H_{12}OCl_2]^{+\cdot}$), 125 (100%, $[C_7H_6Cl]^+$), 77 (35%, $[C_6H_5]^+$), 51 (24%, $[C_4H_3]^+$)	^{1}H NMR δ($CDCl_3$): 2.24 (s, 3H, CH_3), 5.01 (s, 2H, H_d, H_e), 6.75, (d, 1H, $^3J_{HbHa}$=8.7 Hz, H_a), 7.08 (dd, 1H, $^3J_{HbHa}$=8.7 Hz, $^4J_{HbHc}$=2.2 Hz, H_b), 7.13 (d, 1H, $^4J_{HbHc}$=2.2 Hz, H_c), 7.35 (s, 4H, H_{f-i}); ^{13}C NMR δ($CDCl_3$): 16.3 (C_7), 69.5 (C_8), 112.5 (C_6), 126.4 (C_5), 128.5 (C_{11}, C_{13}), 128.8 (C_{10}, C_{14}), 130.6 (C_3)
1-(4-Chlorobenzyloxy)-2-methyl-6-chlorobenzene	C 63.0(62.9); H 5.7(4.5); Cl 26.3(26.5)	266 (5%, $[C_{14}H_{12}OCl_2]^{+\cdot}$), 125 (100%, $[C_7H_6Cl]^+$), 63 (36%, $[C_5H_3]^+$), 51 (40%, $[C_4H_3]^+$)	^{1}H NMR δ($CDCl_3$): 2.26 (s, 3H, CH_3), 4.92 (s, 2H, H_d, H_e), 6.97 (dd, 1H, $^3J_{HbHc}$=$^3J_{HbHa}$=7.8 Hz, H_b), 7.08 (d, 1H, $^3J_{HbHc}$=7.8 Hz, H_c), 7.25 (d, 1H, $^3J_{HbHa}$=7.8 Hz, H_a), 7.37 (d, 1H, $^3J_{Hg,hHf,i}$=8.5 Hz, H_g, H_h), 7.45 (d, 1H, $^3J_{Hg,hHf,i}$=8.5 Hz, H_f, H_i); ^{13}C NMR δ($CDCl_3$): 16.6 (C_7), 73.5 (C_8), 124.9 (C_5), 128.0 (C_6), 128.1 (C_4), 128.7 (C_{11}, C_{13}), 129.5 (C_{10}, C_{14}), 129.6 (C_3), 133.5 (C_2), 134.0 (C_{12}), 135.6 (C_9), 152.9 (C_1)
1-(4-Trifluoromethylbenzyloxy)-2-methylbenzene	C 67.5(67.7); H 5.0(4.9)	266 (25%, $[C_{15}H_{13}OF_3]^{+\cdot}$), 159 (100%, $[C_8H_6F_3]^+$), 77 (10%, $[C_6H_5]^+$)	^{1}H NMR δ($CDCl_3$) 2.30 (s, 3H, CH_3), 5.14 (s, 2H, H_e, H_f), 6.85 (d, 1H, $^3J_{HbHa}$=8.1 Hz, H_a), 6.90 (dd, 1H, $^3J_{HbHc}$=$^3J_{HcHd}$=7.4 Hz, H_c), 7.13–7.19 (m, 2H, H_b, H_d), 7.56 (d, 2H, $^3J_{Hg,jHh,i}$=8.1 Hz, H_g, H_j), 7.65 (d, 2H, $^3J_{Hi,hHg,j}$=8.1 Hz, H_h, H_i); ^{13}C NMR δ($CDCl_3$) 16.4 (C_7), 69.0 (C_8), 111.3 (C_6), 121.0 (C_4), 125.5 (C_{11}, C_{13}), 126.8 (C_5), 127.1 (C_{10}, C_{14}), 130.9 (C_3), 141.6 (C_9), 156.5 (C_1)
1-(4-Trifluoromethylbenzyloxy)-2-methyl-4-chlorobenzene	C 59.7(59.9); H 4.1(4.0); Cl 11.8(11.8)	300 (17%, $[C_{15}H_{12}OClF_3]^{+\cdot}$), 159 (100%, $[C_8H_6F_3]^+$), 77 (16%, $[C_6H_5]^+$), 51 (9%, $[C_4H_3]^+$)	^{1}H NMR δ($CDCl_3$) 2.27 (s, 3H, CH_3), 5.11 (s, 2H, H_d, H_e), 6.75 (d, 1H, $^3J_{HbHa}$=8.7 Hz, H_a), 7.09 (d(d), 1H, $^3J_{HbHa}$=8.7 Hz, $^4J_{HbHc}$=2.7 Hz, Hb), 7.15 (s(d), 1H, $^4J_{HbHc}$=2.7 Hz, H_c); ^{13}C NMR δ($CDCl_3$) 16.2 (C_7), 69.3 (C_8), 112.4 (C_6), 122.8 (C_{12}), 125.6 (C_{11}, C_{13}), 126.4 (C_5), 127.1 (C_{10}, C_{14}), 129.0 (C_2, C_4), 130.7 (C_3), 141.1 (C_9), 155.1 (C_1)
1-(4-Trifluoromethylbenzyloxy)-2-methyl-6-chlorobenzene	C 59.9(59.9); H 4.15(4.0); Cl 12.1(11.8)	300 (8%, $[C_{15}H_{12}OClF_3]^{+\cdot}$), 159 (100%, $[C_8H_6F_3]^+$), 140 (6%, $[C_8H_6F_2]^+$), 77 (12%, $[C_6H_5]^+$), 51 (10%, $[C_4H_3]^+$)	^{1}H NMR δ($CDCl_3$) 2.29 (s, 3H, CH_3), 5.02 (s, 2H, H_d, H_e), 6.99 (dd, 1H, $^3J_{HbHc}$=$^3J_{HbHa}$=7.8 Hz, H_b), 7.10 (d, 1H, $^3J_{HbHc}$=7.8 Hz, H_c), 7.26 (d, 1H, $^3J_{HbHa}$=7.8 Hz, H_a), 7.64 (d, 2H, $^3J_{Hf,iHg,h}$=8.5 Hz, H_f, H_i), 7.66 (d, 2H, $^3J_{Hg,hHf,i}$=8.4 Hz, H_g, H_h); ^{13}C NMR δ($CDCl_3$) 16.5 (C_7), 73.3 (C_8), 122.0 (C12), 125.0 (C_4), 125.4 (C_{11}, C_{13}), 127.9 (C_{10}, C_{14}), 128.2 (C_5), 129.7 (C_3), 133.4 (C_2), 141.1 (C_9), 152.9 (C_1)

Table 2 (*continued*)

Compound name	Microanalysis (%) Found (required)	MS(EI) *m/z*	^{1}H; ^{13}C{^{1}H} NMR δ($CDCl_3$)
1-(4-Nitrobenzyloxy)-2-methyl-4-chlorobenzene	C 60.1(60.6); H 4.6(4.4); N 4.6(5.0)	277 (27%, $[C_{14}H_{12}NO_3Cl]^{+\cdot}$), 136 (100%, $[C_7H_6O_2N]^+$), 106 (38%, $[C_7H_6O]^{+\cdot}$), 78 (45%, $[C_6H_6]^+$), 63 (11%, $[C_5H_3]^+$), 51 (15%, $[C_4H_3]^+$)	^{1}H NMR δ($CDCl_3$) 2.28 (s, 3H, CH_3), 5.16 (s, 2H, H_d, H_e), 6.74 (d, 1H, $^3J_{HaHb}$=8.7 Hz, H_a), 7.10 (d, 1H, $^3J_{HbHa}$=8.7 Hz, $^4J_{HbHc}$=2.6 Hz, H_b), 7.16 (s, 1H, $^4J_{HcHb}$=2.6 Hz, H_c), 7.60 (d, 2H, $^3J_{Hf,iHg,h}$=8.9 Hz, H_f, H_i), 8.26 (d, 2H, $^3J_{Hg,hHf,i}$=8.9 Hz, H_g, H_h); ^{13}C NMR δ($CDCl_3$) 16.3 (C_7), 68.9 (C_8), 112.4 (C_6), 123.9 (C_{11}, C_{13}), 126.1 (C_2), 126.5 (C_5), 127.4 (C_{10}, C_{14}), 129.0 (C_4), 130.9 (C_3), 144.4 (C_9), 147.7 (C_{12}), 154.8 (C_1)
1-(4-Nitrobenzyloxy)-2-methyl-6-chlorobenzene	C 60.4(60.0); H 4.5(4.4); N 4.9(5.0); Cl 12.9(12.8)	277 (45%, $[C_{14}H_{12}NO_3Cl]^{+\cdot}$), 136 (100%, $[C_7H_6O_2N]^+$), 106 (63%, $[C_7H_6O]^{+\cdot}$), 78 (64%, $[C_6H_6]^+$), 63 (19%, $[C_5H_3]^+$), 51 (26%, $[C_4H_3]^+$)	^{1}H NMR δ($CDCl_3$) 2.30 (s, 3H, CH_3), 5.06 (s, 2H, H_d, H_e), 7.01 (dd, 1H, $^3J_{HbHc}$=$^3J_{HbHa}$=7.8 Hz, H_b), 7.11 (d, 1H, $^3J_{HbHc}$=7.8 Hz, H_c), 7.26 (d, 1H, $^3J_{HbHa}$=7.8 Hz, H_a), 7.70 (d, 2H, $^3J_{Hf,iHg,h}$=8.8 Hz, H_f, H_i), 8.27 (d, 2H, $^3J_{Hf,iHg,h}$=8.8 Hz, H_g, H_h); ^{13}C NMR δ($CDCl_3$) 16.5 (C_7), 72.8 (C_8), 123.7 (C_{11}, C_{13}), 125.2 (C_4), 127.9 (C_6), 128.1 (C_{10}, C_{14}), 128.3 (C_5), 129.8 (C_3), 133.3 (C_2), 144.5 (C_9), 147.7 (C_{12}), 152.7 (C_1)

ortho-chloro and some small yet constant amount of dichloro-cresol. Reaction is considerably faster than for the parent *o*-cresol with reactions proceeding to completion within ca. 25 min. We used a slight (5%) excess of *o*-cresol over SO_2Cl_2 in each reaction to ensure complete consumption of the latter and hence avoid any problems of adventitious over chlorination. In Table 1 are collected together $R_{p/o}$ values, conversions and reaction compositions after 25 min in the chlorination of 4′-$XC_6H_4CH_2OC_6H_4$-2-CH_3 (X=H, NO_2, CF_3, Cl, CH_3) with SO_2Cl_2.

It is clear from the position of structural modification that steric effects are envisaged to play a minor, if any role, in influencing regiocontrol. Moreover, even though the data in Table 1 suggest that the nature of substitution has a significant effect upon $R_{p/o}$ values, we must approach such results with care. The proportions of *ortho* and dichloro products are small in each case and with normal considerations of dynamic control effects on high resolution NMR measurements making intensity measurements $<1\%$ unreliable, we are inclined to consider a reliability cut-off $R_{p/o}$ value of ca. 99. Nevertheless, what is incontrovertible is that benzylation of *o*-cresols to afford substituted 1-benzyloxy-2-methyl-benzenes, results in significant increase in selectivity towards *para*-chlorination using SO_2Cl_2, presumably due to the increased steric presence of benzyl substituent blocking access to the remaining phenolic *ortho*-position. Indeed, simple calculations suggest values of $R_{p/o}$ in the region of 50–60 based on the influence of steric factors alone.[†]

Further studies where steric effects are exploited to influence electrophilic aromatic chlorination, primarily through non-covalent interactions, are in progress.

3. Experimental

3.1. General resin methods and techniques

All ^{13}C MAS-CP NMR spectra were collected at 75 MHz with decoupling at 35 kHz and magic angle spinning at 4 kHz using a Bruker MSL-300 spectrometer equipped with 7.1 T magnet and 7 mm DBMAS probe. All spectra were collected with cross polarisation (contact time 1 ms) and therefore are not quantitative.

Merrifield resin (HL 100–200 mesh, loading 1.0–1.6 mmol/g resin) was purchased from NovaBiochem. Sample rotation was achieved using a Fisher Stuart Scientific rotator, in 6 mL volume Isolute Filtration Columns (SPE Accessories from Jones Chromatography) and filtration on 12-Port Vacuum Manifolds (Alltech). Resin pre-washing was performed using high-purity dimethylformamide (DMF). An aliquot of resin (100 mg) was placed in a 6 mL plastic-capped frit-cuvette containing DMF (5 mL) and the cuvette rotated for 1 h. Subsequent filtration on the cuvette under reduced pressure afforded dry resin which was then treated identically a total of eight times over 24 h followed by vacuum oven-drying to constant mass.

Coupling step (i): In a 6 cm^3 column, to the Merrifield resin (600.5 mg, 0.81 mmol) in 2.6 mL of DMF were added *o*-cresol (268 mg, 2.48 mmol), caesium carbonate (792 mg, 2.43 mmol) and sodium iodide (123 mg, 0.82 mmol). The column was rotated at room temperature for 48 h and then washed with 50 mL fractions of DMF, H_2O, DMF, H_2O, acetone, THF and CH_2Cl_2. The resin was dried by vacuum oven to constant mass m=668.3 mg. (Coupling efficiency 87%).

Chlorination step (ii): In a 6 mL column, sulfuryl chloride (27 μL, 0.333 mmol) was added to the *o*-cresol-coupled resin (251.8 mg, 0.337 mmol) in 2 mL of CH_2Cl_2. The column was rotated at room temperature for 2 h, washed with CH_2Cl_2, and vacuum dried to constant mass m=265.3 mg.

Decoupling step (iii): In a 6 mL column, trifluoroacetic acid (1 mL) was added to the resin system above after cresol chlorination (103.6 mg, 0.164 mmol) in 1 mL of CH_2Cl_2. After 2 h rotation at ambient temperature, reaction was quenched with water, the resin washed with both water and CH_2Cl_2 and the filtrate extracted with CH_2Cl_2 (3×10 mL) The organic extracts were then combined, dried over

$MgSO_4$ and all volatiles removed to afford decoupled chlorinated cresols which were analysed subsequently by 500 MHz NMR spectroscopy.

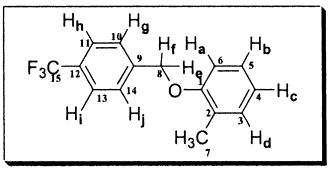
Starting with Merrifield at 1.34 mmol/g loading; replacement of chlorine by *o*-cresol would change theoretical substitution to 1.22 mmol/g using the equation; $S_{th} = S_s/[1 + (S_s Wt_{add})/1000]$ where each of the terms is as described in *Advanced Chemtech Handbook of Combinatorial and Solid Phase Organic Chemistry, A Guide to Principles, Products and Protocols*, Advanced Chemtech, Kentucky, 1998. Subsequently, coupling efficiency is calculated from the equation $C_{eff}=Wt_g/Wt_{ex}$ where Wt_g and Wt_{ex} are the measured and expected (100%) weight gains, respectively.

3.2. General synthetic chemistry

Solvents were HPLC grade and used as received except for dichloromethane which was pre-dried and distilled from calcium hydride and deoxygenated by purging with dinitrogen gas prior to use. Rotation was achieved using a Fisher Stuart Scientific rotator, in 6 mL volume Filtration Columns Isolute, SPE Accessories Jones Chromatography, and filtration on 12-Port Vacuum Manifolds from Alltech. Silica gel used for column chromatography was Fisons Scientific equipment 30–70 mesh, 0.200–0.500 nm. Microanalyses were carried out in the School of Chemistry Microanalysis Laboratory. Mass spectrometric data collected on a VG Autospec instrument (operating at 70 eV for electron impact). Infrared spectra (KBr discs) were collected on MIDAC FT-IR grating Spectrophotometer (4000–600 cm^{-1}). NMR spectra were collected at 298 K on Bruker ARX 250 instrument, Bruker DRX 500 and Bruker AM 400. In all cases the solvent used for NMR was deuterated chloroform $CDCl_3$ (99.8%; 0.03% TMS) and the chemical shifts referenced to residual protons in the solvent or to tetramethylsilane for ^1H and ^{13}C. *o*-Cresol was purchased from G.E. Speciality Chemical and purified by distillation at 76°C under reduced pressure. Sulfuryl chloride was purchased from Fluka.

3.3. Synthesis of substituted 1-benzyloxy-2-methylbenzene ethers

All ethers were prepared by refluxing the chloro-, trifluoro-, nitro-, methyl-benzyl chloride (2 mmol) with an excess of the appropriate *o*-cresol (2.2 mmol) in 5 mL of acetone, and an excess of potassium carbonate in suspension. Reaction times varied from 4 to 48 h. In each case, reaction was quenched with 5 mL of diethylether and 10 mL of water. The mixture was then extracted with diethylether (2×20 mL), the extracts washed with water (2×20 mL) followed by 10% potassium hydroxide (2×10 mL) to remove excess of *o*-cresol and again with water (2×10 mL). The ether extract was subsequently dried over $MgSO_4$, filtered and the volatiles removed under reduced pressure. Purification was generally performed using flash column chromatography on silica. 1-Benzyloxy-2-methylbenzene,[15] 1-(4-nitrobenzyloxy)-2-methyl-benzene,[16] 1-(4-chlorobenzyloxy)-2-methyl-benzene,[17] 1-benzyloxy-4-chloro-2-methyl-benzene,[18] have been described previously. NMR data for all new compounds reflect the general numbering scheme illustrated below for 1-(*para*-trifluoromethylbenzyloxy)-2-methyl-benzene and full data are collected in Table 2.



3.4. Chlorination of benzyl systems

In a Schlenk equipped with a magnetic stirrer, the ether (0.567 mmol) was dissolved in dry CH_2Cl_2 (0.5 mL). Sulfuryl chloride (46 μL, 76.6 mg, 0.567 mmol) was then added at ambient temperature and the mixture stirred under dinitrogen. After 2 h the volatiles were removed under reduced pressure to afford a mixture of benzyl ethers and chlorinated benzyl ethers.

Analysis of this mixture was achieved through 500 MHz ^1H NMR spectroscopy as outlined above and was found to be reproducible to within ±5% (when tested against average of 5 runs). Ratios *R*=*para*/*ortho* were subsequently determined from integration of the peaks in the methyl region of the *o*-cresol, followed by cross-checking against integration of appropriate resonances in the aromatic region. Ratios were calculated by dividing the integration of the methyl of the *para* compound by the integration of the methyl of the *ortho* compound. The percentage conversion is also calculated from integrations of the methyl region of the compounds. If *A* is the value of the integration of the methyl group of the 4-chloro-*o*-cresol, and *B* of the 6-chloro-*o*-cresol, and *T*, the sum of the integration of the methyl of 4-chloro, 6-chloro, 4,6-dichloro-*o*-cresol and the *o*-cresol, so % conversion=$[(A+B)/T]100$.

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