Regioselective synthesis of important chlorophenols in the presence of methylthioalkanes with remote SMe, OMe or OH substituents

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ABSTRACT

Various methylthio alcohols, methoxy(methylthio)alkanes and *bis*(methylthio)alkanes have been used as regioselectivity modifiers in the chlorination reactions of various phenols at room temperature. The process involves use of a slight excess of sulfuryl chloride in the presence of aluminum or ferric chloride as an activator. Methylthio alcohols, methoxy(methylthio)alkanes and *bis*(methylthio)alkanes having 2 and 3 methylene groups as a spacer were found to be good for the *para*-selective chlorination of *o*-cresol and phenol. On the other hand, methylthio alcohols, methoxy(methylthio)alkanes and *bis*(methylthio)alkanes having 6 and 9 methylene groups were found to be good for the selective *para*-chlorination of *m*-xylenol and *m*-cresol. Calculations using density functional theory on *bis*(methylthio)alkanes have suggested two different types of stable chlorinated intermediates depending on the number of methylene units as a spacer.

KEYWORDS Regioselective chlorination; Methylthio alcohols; Methoxy(methylthio)alkanes; *bis*(Methylthio)alkanes; Phenols

1. Introduction

Chlorinated phenols are important intermediates for many pharmaceutical and industrial products [1,2]. Also, they act as commercial disinfectants and household active ingredients and have to be isomerically pure to avoid problems associated with use of chlorinated phenol mixtures. Therefore, the development of selective chlorination processes for simple phenols is highly desirable, both in its own right and to reduce the waste from use of traditional procedures [3–5].

Various procedures have been reported for improving the selectivity of chlorination reactions of phenols. For example, chlorination of phenol over an Al-pillared montmorillonite clay using freshly distilled sulfuryl chloride (SO_2Cl_2) in 2,2,4-trimethylpentane as solvent at 25 °C gave 4-chlorophenol in 76% yield and a *para*/*ortho* ratio of 5.7, while reaction under similar conditions in the presence of partially cation-exchanged L type zeolite gave 4-chlorophenol in 85% yield and a *para*/*ortho* ratio of 8, compared to a *para*/*ortho* ratio of only 1.7 when reaction was carried out in the absence of the clay [6]. Chlorination of *o*-cresol attached to Merrifield resin with sulfuryl chloride in dichloromethane (DCM), followed by a trifluoroacetic acid (TFA) decoupling step, was more selective, giving *p*-chloro-*o*-cresol in high yield with a *para*/*ortho*

ratio of *ca*. 50 [7]. However, the reaction has been applied on only a very small scale (0.33 mmol of *o*-cresol) and also involves several steps, solvents, reagents and a relatively large quantity of Merrifield resin, so is not attractive for commercial application. As a result of the commercial importance of the products, regioselective halogenation of phenols continues to attract attention [8–16] and there is still a need for convenient yet highly selective processes.

Chlorination of phenols over sulfur containing compounds in the presence of metal halides [17–19] offers considerable potential for regioselectivity. For example, use of diphenyl sulfide in the presence of aluminum chloride ($AlCl_3$) in chlorination of *o*-cresol with sulfuryl chloride gave mainly *p*-chloro-*o*-cresol with a *para/ortho* ratio of *ca*. 20 [17,18]. We have previously shown that simple aliphatic sulfides can also improve *para*-selectivity in chlorination reactions of phenols with sulfuryl chloride [20,21]. Unfortunately, some examples of such sulfides are volatile and not desirable for use in commercial application. However, such volatility was overcome by the use of modified Merrifield resins or dithiaalkanes [22,23]. As part of our continued interest in the use of solid catalysts in regioselective aromatic electrophilic substitution reactions [24–27], we recently showed that cyclic or polymeric disulfides could also be used to improve regioselectivity in chlorination of phenols [28].

The conventional wisdom is that sulfur compounds give greater *para*-selectivity in chlorination of phenols by forming bulky chlorosulfonium salts that can more readily approach the more distal *para*-position than the proximal *ortho*-position of the phenol [17]. However, some of our results did not appear to fit very well with this conventional understanding. Therefore, we decided to investigate the use of different sulfur containing compounds that could help probe the effect of sulfur groups in chlorination reactions of phenols. In the present work we report the use of a range of methylthio alcohols, methoxy(methylthio)alkanes and *bis*(methylthio)alkanes in chlorination reactions of various phenols. We have also attempted to understand the chlorinated intermediates that might be formed when *bis*(methylthio)alkanes are used as additives by the use of density functional theory (DFT) calculations of the structures of the reactive intermediates.

2. Results and discussion

The ability of the hydroxyl group of phenols to interact through hydrogen bonding with electronegative atoms has been utilized in selective *ortho*- or *para*-chlorinations of phenol [29].

One working hypothesis for some of the unexpected results that we had observed previously with dithiaalkanes was that there was interaction between the phenolic OH group and one sulfur atom, which resulted in a chlorosulfonium group located at the other end of a spacer group being located closer to one potential reaction site than to another. However, the hydrogen bonding between a phenolic OH group and a methylthio group is not expected to be very strong and a stronger interaction (and perhaps greater regioselectivity as a result) might be expected from a methoxy or hydroxyl group. Therefore, we have prepared a range of methylthioalkylene derivatives with different alkylene spacer groups and three different remote substituents, namely OH, OMe and SMe (Fig. 1) and investigated their use as additives in the chlorination of phenols. We would expect the three different substituents to show different hydrogen bonding abilities, which would presumably cause different regioselectivity in chlorination reactions moderated by the different compounds. In particular, we would expect the hydrogen-bonding to a phenolic hydroxyl group to diminish in the order OH, OMe, SMe.

Methylthio alcohols [30–33] having 2–9 methylene groups (Fig. 1) were prepared from the corresponding hydroxyalkylenethiols using one mole equivalent of methyllithium followed by the addition of one mole equivalent of iodomethane, while the corresponding methoxy(methylthio)alkanes [34,35] were prepared from the same starting materials using two mole equivalents of MeLi followed by the addition of two mole equivalents of MeI. *bis*(Methylthio)alkanes [36,37] having 2–9 methylene groups (Fig. 1) were prepared from the corresponding dithiols using two mole equivalents of MeLi followed by the addition of two mole equivalents of MeI.

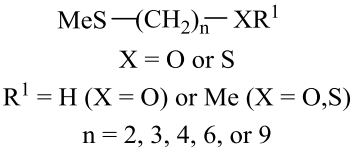
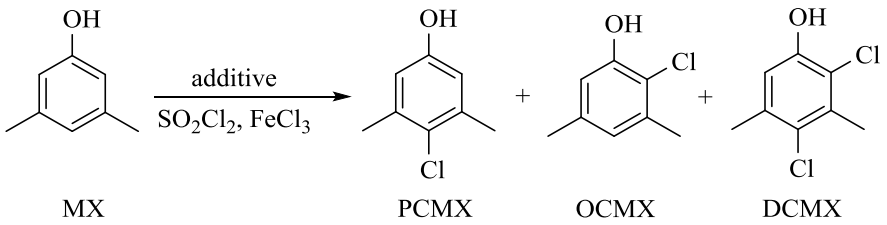


Fig. 1. The structures of methylthioalkyl sulfides, ethers and alcohols prepared in this study.

In view of the importance of 4-chloro-3,5-dimethylphenol (*para*-chloro-*meta*-xylenol, PCMX) as a commercial disinfectant, we first attempted chlorination of *m*-xylenol (50 mmol) with sulfuryl chloride (57.7 mmol) (Scheme 1) in the presence of methylthio alcohols (30 mg) and $FeCl_3$ (25 mg) in dichloromethane (DCM, 25 mL). $FeCl_3$ was chosen instead of $AlCl_3$ as the

Lewis acid because the commercial specification for the product requires a low Al content. The results obtained are recorded in Table 1, which also includes baseline results for chlorination of *m*-xylenol in the absence of any additive for comparison.



Scheme 1. Chlorination of *m*-xylenol.

Table 1. Chlorination of *m*-xylenol in the presence of methylthio alcohols and $FeCl_3$.[a]

$MeS(CH_2)_nOH$ (n)	Yield (%)[b]				*p/o* ratio	Mass balance (%)[c]
	MX	OCMX	PCMX	DCMX		
—	3.0 (4.5)	10.0 (11.3)	84.6 (82.0)	0.2 (1.0)	8.4 (7.2)	98.8 (98.3)
2	2.0	14.0	80.0	4.0	5.7	100.0
3	2.9	15.0	80.0	2.5	5.3	100.4
4	2.8	15.5	79.3	2.1	5.1	99.7
6	2.2	4.6	90.0	3.2	19.5	100.0
9	0.8	4.7	91.0	3.2	19.4	99.7

[a] SO_2Cl_2 (4.66 mL, 57.7 mmol) was slowly added to a mixture of *m*-xylenol (6.11 g, 50.0 mmol), $FeCl_3$ (25 mg) and the organic additive (30 mg) in DCM (25 mL) at room temperature over 2 h and the mixture was stirred for 2 h before it was worked-up.
[b] Yield percentage was calculated using quantitative GC. Figures in parentheses are for the reaction carried out in the absence of $FeCl_3$.
[c] Sum of the yields of all identified compounds.

The results recorded in Table 1 clearly indicate that 6-(methylthio)hexanol (n = 6) and 9-(methylthio)nonanol (n = 9) gave better *para/ortho* ratios and higher yields of the *para*-isomer (90% and 91%, respectively) than when no additive was used. On the other hand, additives where n = 2–4 behaved in different manner and gave lower yields of PCMX (*ca*. 80%) and lower *para/ortho* ratios even than for the reaction when no additive was present.

Therefore, it did seem that the presence of the OH group had been influential in affecting the selectivity of the additive. It seemed from these results that it was indeed possible that the OH group was hydrogen bonding to the phenolic OH group. The longer spacer group could then allow the SMe group, bearing the chlorine to be transferred to the ring, to reach around to the distant *para*-position, allowing greater *para*-selectivity, if the reaction is intramolecular. By

contrast, the shorter spacer groups may restrict the reach of the chlorine-bearing SMe group, thereby enhancing the *ortho*-isomer in comparison to the situation when there is no additive. However, a complicating feature could be that some of the alcohol additive may have been converted to other species under the reaction conditions, so methoxy(methylthio)alkanes (n = 2–4, 6 and 9) were next investigated as additives under conditions similar to those used with methylthio alcohols. The results are recorded in Table 2.

Table 2. Chlorination of *m*-xylenol in the presence of methoxy(methylthio)alkanes and $FeCl_3$.[a]

$MeS(CH_2)_nOMe$	Yield (%)[b]				*p/o* ratio	Mass balance
(n)	MX	OCMX	PCMX	DCMX		(%)[c]
—	3.0 (4.5)	10.0 (11.3)	84.6 (82.0)	0.2 (1.0)	8.4 (7.2)	97.8 (98.8)
2	3.8	11.7	80.5	3.8	6.8	99.8
3	2.1	5.2	89.1	1.9	17.1	98.3
4	4.4	9.0	85.0	1.8	9.4	100.2
6	2.2	5.4	90.0	2.1	16.6	99.7
9	1.9	3.5	92.4	1.9	26.4	99.7

[a,b,c] See footnotes to Table 1.

It is obvious from Table 2 that methoxy(methylthio)alkanes where n = 3, 6 or 9 gave higher *para*-selectivity than the ones where n was 2 or 4. In general, the additives with shorter spacer groups were not as low in *para*-selectivity as the corresponding hydroxy(methylthio)alkanes, which could be consistent with the H-bonding hypothesis (the methoxy additives being less tightly held). However, on the basis of that hypothesis it is not clear why methoxy(methylthio)alkane additives with n = 3 and n = 9 would be ***more*** *para*-selective than the corresponding hydroxy(methylthio)alkanes.

Next, *bis*(methythio)alkanes (n = 2–4, 6 and 9) were used as additives for the chlorination of *m*-xylenol. The results obtained are recorded in Table 3.

Table 3. Chlorination of *m*-xylenol in the presence of *bis*(methythio)alkanes and $FeCl_3$.[a]

$MeS(CH_2)_nSMe$	Yield (%)[b]				*p/o* ratio	Mass balance
(n)	MX	OCMX	PCMX	DCMX		(%)[c]
—	3.0 (4.5)	10.0 (11.3)	84.6 (82.0)	0.2 (1.0)	8.4 (7.2)	97.8 (98.8)
2	6.2	9.7	76.6	7.3	7.8	99.8
3	5.8	10.0	75	9.0	7.5	99.8
4	3.1	16.0	73.0	7.3	4.5	99.4
6	3.9	4.4	86.6	4.9	19.6	99.8
9	1.9	5.9	90.0	1.9	15.2	99.7

[a,b,c] See footnotes to Table 1.

A complicating feature of the results in Table 3 is the relatively high proportion of DCMX formed in several of the reactions under the standard conditions used. Since there is no information about the relative reactivity of the two monochloroxylenols (OCMX and PCMX), some caution must be exercised in interpreting the actual *p/o* ratios. Notwithstanding that caveat, Table 3 shows that the selectivity with *bis*(methylthio)alkanes having n = 6 and 9, which gave yields of PCMX of 86.6 and 90% respectively, was similar to the selectivity with both methylthio alcohols and methoxy(methylthio)alkanes with the same spacer lengths. *bis*(Methylthio)alkanes with n = 2 and 3 gave similar results to reactions without any additive, while the *para*-selectivity of *bis*(methylthio)butane (n = 4) was less (*para/ortho* ratio was 4.5) than for the case where no additive was used.

In summary, the general trend was for the *para*-selectivity to increase with increasing spacer length from 2 to 9 for all three types of additives, which is broadly consistent with the notion that hydrogen bonding between the phenolic OH group and the heteroatom of the additive causes the active chlorination site on the remote sulfur atom to be located more conveniently for intramolecular *para*-substitution for longer spacer groups. However, the *para*-selectivity with methoxy(methylthio)propane was significantly higher than was obtained from use of other types of additives where n = 3, while the selectivity obtained from use of additives where n = 4 was lower in all cases than with the same type of additive with n = 3 or 6, and in two of the three cases was lower than for the reaction without any additive. This latter result could be consistent with the hydrogen-bonding hypothesis if a chain length of four methylene groups provides the optimum separation of the Cl-bearing S atom from the H-bonded heteroatom for delivery of the Cl to the *ortho*-position, although in all cases it should be noted that *para*-substitution still predominates. Alternatively, perhaps the effect could be explained by the 4-carbon spacer having the optimal length to allow interaction between the two heteroatoms in a pseudo six-membered ring (Fig. 2). In such cases the heteroatom could interact *via* overlap between a lone pair of electrons on the heteroatom and a vacant d-orbital on sulfur. This interaction could shield the sulfur atoms so that they are less available for chlorination by SO_2Cl_2 than for an open chain arrangement, or alternatively, when the species is chlorinated by SO_2Cl_2 it could behave differently in terms of its steric hindrance than is the case when it is open chain.

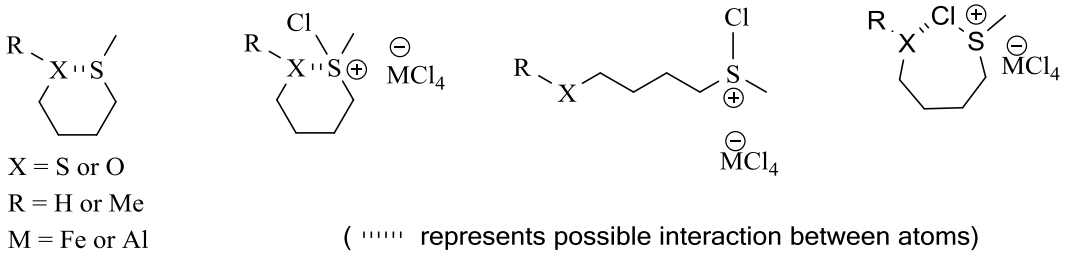
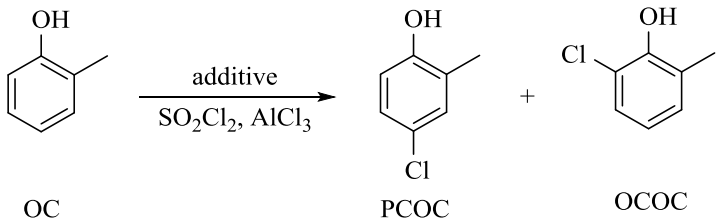


Fig. 2. Possible interaction between heteroatoms of additive in the presumed active species.

In order to investigate whether the distant heteroatom of the additive was a major cause of the low selectivity for the cases when n = 4, or whether it was simply a reflection of the overall size of the additive in those cases, chlorination of *m*-xylenol was carried out in the presence of hexyl methyl sulfide (30 mg) as additive under similar conditions to those reported in Tables 1–3. The ethyl unit at the end of the hexyl chain is roughly equivalent in size to the OMe or SMe group of other types of additive, but would not be able to hydrogen bond at all to the phenolic OH group. The hexyl methyl sulfide showed modestly improved selectivity compared to baseline results, giving an 86% yield of PCMX and a *para/ortho* ratio of 10.2 (equivalent to a *para:ortho* ratio of 20.4 if consideration given to the fact that there are two equivalent *ortho* positions and only one *para* position in *m*-xylenol). This result represents higher *para*-selectivity than for any of the other additives with n = 4, consistent with the hypothesis that hydrogen bonding of the remote heteroatom to the phenolic OH group (absent in hexyl methyl sulfide) enhances *ortho*-substitution, although the result with methoxy(methylthio)butane as additive showed only a small difference from methylthiohexane.

It was hoped that more clues might emerge following studies of the chlorination of other phenols. We have previously shown that aluminum chloride and ferric chloride behave very similarly in sulfur compound moderated chlorinations of phenols,[21] but the reactions with $AlCl_3$ are generally slightly more *para*-selective. Therefore, reactions with phenols other than *meta*-xylenol were conducted with $AlCl_3$ as Lewis acid co-additive, rather than $FeCl_3$. Also, since the other phenols studied were liquid or easily liquefied around ambient temperature, the reactions were conducted in the absence of solvent, which would be more akin to conditions used in commercial chlorinations.

Chlorination of *o*-cresol in the presence of the various additives was next undertaken. A mixture of the additive (0.10 g), *o*-cresol (50 mmol) and $AlCl_3$ (0.25 g) was treated with sulfuryl chloride (57.7 mmol) in the absence of solvent (Scheme 2). The results are given in Tables 4–6.



Scheme 2. Chlorination of *o*-cresol.

Table 4. Chlorination of *o*-cresol in the presence of methylthio alcohols and $AlCl_3$.[a]

$MeS(CH_2)_nOH$	Yield (%)[b]			*p/o* ratio	Mass balance
(n)	OC	OCOC	PCOC		(%)[c]
—	14.0 (15.0)	9.0 (9.3)	76.0 (75.6)	8.4 (8.1)	99.0 (99.8)
2	3.9	6.0	90.0	15.0	99.9
3	2.5	6.2	91.2	14.7	99.9
4	4.5	22.8	72.5	3.1	99.8
6	5.9	7.8	86.2	11.0	99.9
9	2.0	13.0	84.8	6.5	99.8

[a] SO_2Cl_2 (4.66 mL, 57.7 mmol) was slowly added to a mixture of *o*-cresol (5.41 g, 50.0 mmol), $AlCl_3$ (0.25 g) and organic additive (0.10 g) at room temperature over 2 h and the mixture was stirred for another 2 h before it was worked-up.
[b] Yield percentage was calculated using quantitative GC. Figures in parentheses are for the reaction carried out in the absence of $AlCl_3$.
[c] Sum of the yields of all identified compounds.

Table 5. Chlorination of *o*-cresol in the presence of methoxy(methylthio)alkanes and $AlCl_3$.[a]

$MeS(CH_2)_nOMe$	Yield (%)[b]			*p/o* ratio	Mass balance
(n)	OC	OCOC	PCOC		(%)[c]
—	14.0 (15.0)	9.0 (9.3)	76.0 (75.6)	8.4 (8.1)	99.0 (99.8)
2	1.0	4.7	94.0	20.0	99.7
3	1.6	5.4	93.4	18.0	100.0
4	5.2	8.6	86.0	10.0	99.8
6	1.2	5.0	93.5	18.7	99.7
9	3.3	10.7	85.8	8.0	99.8

[a,b,c] See footnotes to Table 4.

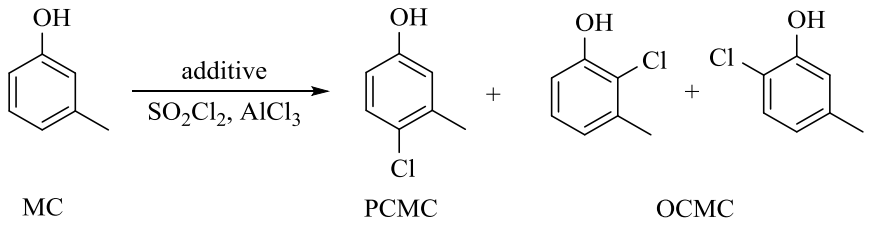
Table 6. Chlorination of *o*-cresol in the presence of *bis*(methythio)alkanes and $AlCl_3$.[a]

$MeS(CH_2)_nSMe$ (n)	Yield (%)[b]			*p/o* ratio	Mass balance (%)[c]
	OC	OCOC	PCOC		
—	14.0 (15.0)	9.0 (9.3)	76.0 (75.6)	8.4 (8.1)	99.0 (99.8)
2	0.9	4.5	94.4	20.9	99.8
3	2.4	2.4	95.0	39.5	99.8
4	1.3	10.5	88.1	8.3	99.9
6	2.1	6.0	92.0	15.3	100.0
9	2.7	14.3	82.9	5.7	99.9

[a,b,c] See footnotes to Table 4.

It is clear from Tables 4–6 that the picture for chlorination of *o*-cresol is very different than for chlorination of *m*-xylenol. In the case of *o*-cresol the general trend is for *para*-selectivity to reduce as the length of the spacer group increases for all three types of additive, exactly the opposite trend to that seen for *m*-xylenol, suggesting that H-bonding is not the major contributor to the regiosoelectivity in this case. However, the *para*-selectivity with additives having n = 4 is invariably lower than for the corresponding additives with n = 3 or n = 6, showing again that the case of n = 4 is somewhat special. Chlorination of *o*-cresol (50 mmol) was also carried out using hexyl methyl sulfide (100 mg) as additive in the presence of $AlCl_3$ and gave PCOC in 82% yield with a *para/ortho* ratio of 8.2. These results are similar to those obtained with no additive or with methoxy(methylthio)butane or *bis*(methylthio)butane as additive, but 4-(methylthio)butanol was significantly less *para*-selective than all of those cases, again consistent with the notion that the strongest hydrogen bonding additive might increase the amount of attack at the *ortho*-position.

The various additives (0.10 g) were next investigated in chlorination of *m*-cresol (50 mmol) with sulfuryl chloride (57.7 mmol) in the presence of $AlCl_3$ (0.25 g) in the absence of any solvent (Scheme 3). The results obtained are recorded in Tables 7–9.



Scheme 3. Chlorination of *m*-cresol.

Table 7. Chlorination of *m*-cresol in the presence of methylthio alcohols and $AlCl_3$.[a]

$MeS(CH_2)_nOH$ (n)	Yield (%)[b,c]			*p/o* ratio	Mass balance (%)[d]
	MC	OCMC	PCMC		
—	2.5 (3.2)	9.5 (10.0)	87.2 (86.0)	9.1 (8.6)	99.2 (99.2)
2	3.8	10.0	86.0	8.6	99.8
3	0.6	9.0	89.0	9.8	99.6
4	1.3	9.5	89.1	9.3	99.8
6	0.6	6.4	93.0	14.5	100.0
9	0.2	6.2	93.0	15.0	99.8

[a] SO_2Cl_2 (4.66 mL, 57.7 mmol) was slowly added over 2 h to a mixture of *m*-cresol (5.41 g, 50.0 mmol), $AlCl_3$(0.25 g) and organic additive (0.10 g) at room temperature and the mixture was stirred for another 2 h before it was worked-up.
[b] Yield percentage was calculated using quantitative GC. Figures in parentheses are for the reaction carried out in the absence of $AlCl_3$.
[c] The two *ortho*-chlorinated products have been grouped under the banner OCMC because the two isomers could not be separated with the GC system used.
[d] Sum of the yields of all identified compounds.

Table 8. Chlorination of *m*-cresol in the presence of methoxy(methylthio)alkanes and $AlCl_3$.[a]

$MeS(CH_2)_nOMe$ (n)	Yield (%)[b,c]			*p/o* ratio	Mass balance (%)[d]
	MC	OCMC	PCMC		
—	2.5 (3.2)	9.5 (10.0)	87.2 (86.0)	9.1 (8.6)	99.2 (99.2)
2	4.2	10.7	85.0	7.9	99.9
3	2.3	8.0	89.6	11.2	99.9
4	4.0	9.0	87.0	9.6	100
6	0.7	6.0	93.2	15.5	99.9
9	0.0	6.1	93.9	15.3	100.0

[a,b,c,d] See footnotes to Table 7.

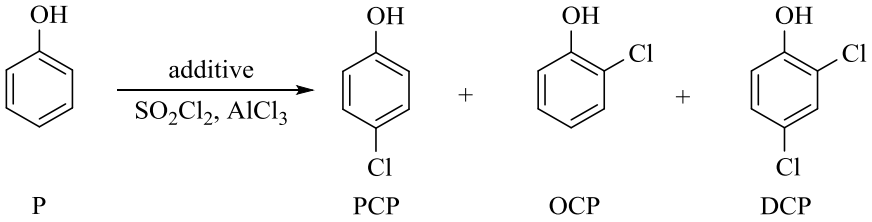
Table 9. Chlorination of *m*-cresol in the presence of *bis*(methythio)alkanes and $AlCl_3$.[a]

$MeS(CH_2)_nSMe$ (n)	Yield (%)[b,c]			*p/o* ratio	Mass balance (%)[d]
	MC	OCMC	PCMC		
—	2.5 (3.2)	9.5 (10.0)	87.2 (86.0)	9.1 (8.6)	99.2 (99.2)
2	4.8	10.3	84.7	8.2	99.8
3	5.0	8.5	86.4	10.6	99.9
4	1.9	7.4	90.5	12.2	99.8
6	0.5	5.4	93.9	17.3	99.8
9	0.2	5.2	94.0	18.0	99.4

[a,b,c,d] See footnotes to Table 7.

From Tables 7–9 it is clear that the general trend with *m*-cresol is for increasing *para*-selectivity as the spacer group length increases, which is the same as for *m*-xylenol but the opposite of that observed for *o*-cresol. Again, the situation with additives having a tetramethylene spacer group was out of line with the general trend; for two of the additive types, the selectivity was lower with n = 4 than that observed for the corresponding additives with either n = 3 or n = 6, while for *bis*(methylthio)butane the value was between the values for *bis*(methylthio)propane and *bis*(methylthio)hexane. The *bis*(methylthio)alkane additives were generally a little more *para*-selective than the other two types, except for those with the shortest spacer groups, for which all three types were rather similar. With methyl hexyl sulfide (0.10 g) as additive in the presence of $AlCl_3$ (0.25 g) the yield of PCMC was 92% and the *para/ortho* ratio was 18.4, *i.e.* selectivity was almost as good as with the best of the other additives, suggesting that hydrogen bonding was not the primary factor influencing selectivity.

The chlorination of phenol (50 mmol) was next investigated in the presence of the various organic additives and of $AlCl_3$ (Scheme 4). The results are recorded in Tables 10–12.



Scheme 4. Chlorination of phenol.

Table 10. Chlorination of phenol in the presence of methylthio alcohols and $AlCl_3$.[a]

$MeS(CH_2)_nOH$ (n)	Yield (%)[b]				*p/o* ratio	Mass balance (%)[c]
	P	OCP	PCP	DCP		
—	6.0 (6.5)	19.0 (20.2)	73.0 (71.0)	2.0 (1.5)	3.8 (3.5)	100.0 (99.2)
2	1.0	13.0	83.0	2.8	6.3	99.8
3	0.0	32.0	64.0	3.7	1.9	99.8
4	5.2	23.0	69.3	2.3	3.0	99.8
6	3.1	13.0	82.1	1.5	6.3	99.7
9	2.0	12.7	83.1	2.0	6.5	99.8

[a] SO_2Cl_2 (4.66 mL, 57.7 mmol) was slowly added to a mixture of phenol (4.71 g, 50.0 mmol), $AlCl_3$ (50 mg) and the organic additive (50 mg) at room temperature over 2 h and the mixture was stirred for another 4 h before it was worked-up.
[b] Yield percentage was calculated using quantitative GC. Figures in parentheses are for the reaction carried out in the absence of $AlCl_3$.
[c] Sum of the yields of all identified compounds.

Table 11. Chlorination of phenol in the presence of methoxy(methylthio)alkanes and $AlCl_3$.[a]

$MeS(CH_2)_nOMe$	Yield (%)[b]				*p/o* ratio	Mass balance
(n)	P	OCP	PCP	DCP		(%)[c]
—	6.0 (6.5)	19.0 (20.2)	73.0 (71.0)	2.0 (1.5)	3.8 (3.5)	100.0 (99.2)
2	2.3	11.6	83.5	2.3	7.1	99.7
3	3.0	18.0	76.0	2.1	4.2	99.1
4	0.6	13.0	84.6	1.6	6.5	99.8
6	3.3	11.0	85.0	0.0	7.7	99.3
9	1.0	9.5	88.0	1.6	9.2	100

[a,b,c] See footnotes to Table 10.

Table 12. Chlorination of phenol in the presence of *bis*(methythio)alkanes and $AlCl_3$.[a]

$MeS(CH_2)_nSMe$	Yield (%)[b]				*p/o* ratio	Mass balance
(n)	P	OCP	PCP	DCP		(%)[c]
—	6.0 (6.5)	19.0 (20.2)	73.0 (71.0)	2.0 (1.5)	3.8 (3.5)	100.0 (99.2)
2	4.4	8.3	87.3	0.0	10.5	99.7
3	3.7	7.7	88.4	0.0	11.4	99.8
4	0.6	8.2	88.8	2.3	10.2	99.9
6	2.0	12.0	84.5	1.5	7.0	100
9	1.5	9.7	87.0	1.6	9.2	99.7

[a,b,c] See footnotes to Table 10.

From Tables 10–12 it is clear that methylthio alcohols and methoxy(methylthio)alkanes exhibit similar trends in selectivity for chlorination of phenol, but with the methoxy compounds possibly being somewhat more *para*-selective. In both series the selectivity was higher when n = 2, 6 and 9, for which cases they provided significantly greater *para*-selectivity than for the chlorination of phenol in the absence of any additive, while the lowest selectivity in both series was for a spacer group length of n = 3. Indeed, methylthioalcohols with n = 3 and 4 gave even lower *para/ortho* ratios than when no additive was used (*para/ortho* = 3.5–3.8). By contrast, the *para*-selectivity of *bis*(methylthio)alkanes peaked when n = 2–4 and was higher than for the other two types of additive for the same spacer group length in almost all cases.

Chlorination of phenol in the presence of methyl hexyl sulfide under comparable conditions gave PCP in 81% yield and a *para/ortho* ratio of 6.5, which is comparable to the selectivity with methoxy(methylthio)butane, but less than that with *bis*(methylthio)butane, each of which is roughly equivalent in overall size. The additives with spacer groups having n = 4

were not so out of line with those having other spacer group lengths in the chlorination of phenol as they were for chlorination of the methyl-substituted phenols.

If the results for all four phenols are considered together, some trends emerge. First, in all four cases the trends for the methylthio alcohols and the methoxy(methylthio)alkanes are very similar and generally the methoxy compounds give somewhat higher *para*-selectivity than the alcohols, although the variation in selectivity is not significant enough to allow firm conclusions to be drawn, especially if the possibility of the alcohols reacting to some extent under the reaction conditions is considered. Therefore, the results cannot definitely rule out the hydrogen-bonding and intramolecular transfer of chlorine hypothesis, but they do not really support the view that H-bonding between the distant heteroatom and the phenolic OH group helps deliver the active chlorine to a location appropriately distant from the phenolic OH group. Furthermore, *bis*(methylthio)alkanes are often more *para*-selective than either of the other types of additive, although the methylthio group would be the weakest at H-bonding to the phenolic OH.

Second, the trends for *m*-xylenol and *m*-cresol are rather similar, with the highest *para*-selectivity being observed with the longer spacer groups (n = 6 and 9). By contrast, the trend for *o*-cresol is almost the opposite. Although the differences are less marked, the best *para*-selectivity for this substrate is observed with the short spacer groups (n = 2 and 3). The situation with phenol itself is less clear cut. The trends for methythio alcohols and methoxy(methylthio)alkanes are similar to those for *m*-xylenol and *m*-cresol (highest *para*-selectivity for n = 6 or 9), while with the *bis*(methylthio)alkanes the trend is more like that for *ortho*-cresol (selectivity better for short spacer groups).

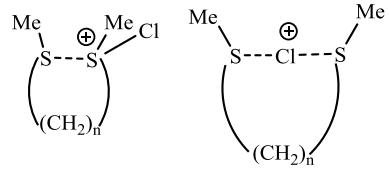
Third, in the cases of methyl-substituted phenols there is a dip in the *para*-selectivity for additives with tetramethylene spacer groups (n = 4) for almost all additives with each of the substrates. However, the situation is not as clear cut for chlorination of phenol.

Computational study

Since these trends are not easy to interpret in terms of any single factor, they may suggest that different influences are bearing on the reactions in different cases. Although the differences in observed selectivity are synthetically significant, the implied differences in transition state energies are rather small. Given the complexity of the systems (up to 13 non-H atoms in an open chain additive, together with a phenol, a chlorination source and a Lewis acid) and the small

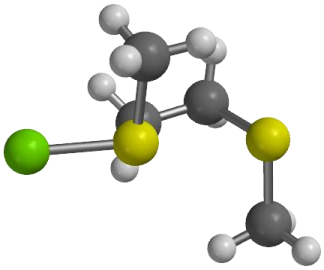
energy differences that would need to be explained, it was not possible to get meaningful transition state information by use of calculations. However, it was possible to attempt to gain further insight into the nature of the active species by use of calculations using the Spartan '10 computational package and since the *bis*(methylthio)alkanes are generally the most *para*-selective of the additives, they were chosen for the study.

Potential intramolecular interactions between the heteroatoms were initially probed using semi-empirical calculations (AM1 and PM6). Gas phase calculations on mono-chlorinated *bis*(methylthio)alkanes ($[MeS(CH_2)_nSMe]Cl^+$) suggested two different types of stable chlorinated intermediate. Optimization of the lowest energy structure of each type using DFT (Density Functional Theory) at the B3LYP/6-31G* level suggested that for compounds having shorter spacer groups (n = 2–4) the more stable intermediates would involve S–S–Cl interactions (Fig. 3), while the intermediates in the cases of the longer spacer groups (n ≥ 6) would involve S–Cl–S interactions (Table 13). On the suggestion of a referee, we repeated these calculations using a larger basis set [6-311+G(3D,3P)], through the Gaussian suite of programs. The calculated energy differences between the two types of intermediates were somewhat altered (generally the S–S–Cl form was lowered in energy relative to the S–Cl–S form compared to the calculations using the smaller basis set), but the differences were not great enough to affect the conclusions.

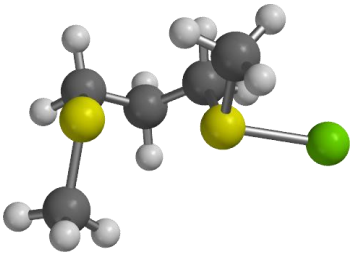


n = 2,3 or 4
(S–S–Cl type)

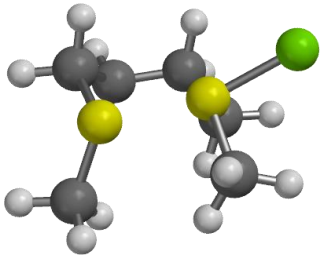
n = 6 or more
(S–Cl–S type)

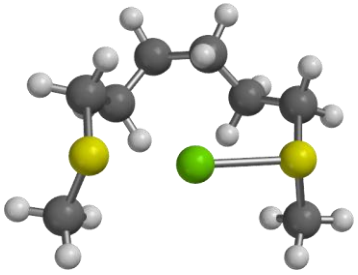


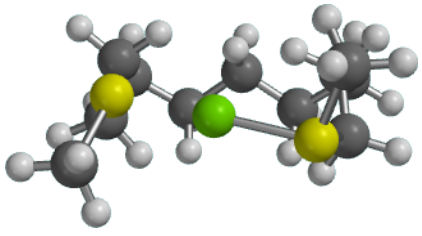
n = 2 (S–S–Cl)



n = 3 (S–S–Cl)







n = 4 (S–S–Cl)

n = 6 (S–Cl–S) n = 9 (S–Cl–S)

Fig. 3. The more stable type of the chlorinated *bis*(methylthio)alkane intermediates with n = 2, 3, 4, 6 and 9 according to DFT calculations.

Table 13. S–S–Cl and S–Cl–S energy differences for $[MeS(CH_2)_nSMeCl]^+$.

n in $[MeS(CH_2)_nSMeCl]^+$	Energy difference (B3LYP) (kJ mol^{-1})
2	S–Cl–S not found
3	S–Cl–S not found
4	35.7 (S–S–Cl more stable)
6	23.1 (S–Cl–S more stable)
9	45.5 (S–Cl–S more stable)

It is possible that different kinds of reactive intermediate such as these may offer some insight into why additives with longer spacer groups are more *para*-selective than those with shorter spacer groups for certain phenols (*e.g*. *m*-cresol and *m*-xylenol), while those with shorter spacer groups are more *para*-selective for other phenols (*e.g*. *o*-cresol). These ideas would justify further investigation in future.

3. Conclusion

The spacer group lengths of the prepared compounds play important roles in the selectivity properties displayed when those compounds are used as additives in chlorination reactions of various phenols. For example, methylthio alcohols, methoxy(methylthio)alkanes and *bis*(methylthio)alkanes with n = 2 and 3 are good for the selective *para*-chlorination of *o*-cresol, while the corresponding compounds with n = 6 and 9 are good for the selective *para*-chlorination of *m*-xylenol and *m*-cresol.

The computational study of the structures of the chlorinated *bis*(methylthio)alkanes with different spacer group lengths has suggested that the chlorinated sulfide additives with n = 2 and 3 have a S–S–Cl structure while those with n = 6 and 9 have a S–Cl–S structure. This difference might be responsible for the different performances with different phenols of these two groups of additives, but it is not entirely clear how the structures bring about those differences. Further

research is needed in order to provide an understanding of the selectivity effects of the different spacer group lengths in these kinds of species.

4. Experimental

4.1 General

Chemicals and phenol derivatives were purchased from Aldrich and Lancaster Chemicals and used without further purification. All GC analyses were carried out on a Shimadzu GC-2014 Gas Chromatograph using a capillary ZB Carbowax column (30 m, 0.32 mm ID). The GC conditions used for analysis were as follows: 40 °C for 3 min, ramped to 220 °C at 10 °C/min and held for 8 min. The injection temperature was 300 °C and the detection temperature 250 °C. Tetradecane was added as an internal standard to allow quantification. All of the expected products from chlorination of phenols were purchased from Aldrich Chemical Company and used to determine retention times and response factors relative to tetradecane (average from four injections) for each product.

Methythio alcohols [30–33] methoxy(methythio)alkanes [34,35] and *bis*(methythio)alkanes [36,37] were prepared based on literature procedures and their spectroscopic data were consistent with those reported [30–37].

4.2 Typical experimental procedure for the chlorination of m-xylenol

Freshly distilled sulfuryl chloride (4.66 mL, 57.7 mmol) was added slowly over 2 h, *via* a pressure equalising dropping funnel, to a solution of *m*-xylenol (6.1 g, 50 mmol), $FeCl_3$ (25 mg, 0.154 mmol) and an additive (30 mg) in dichloromethane (DCM, 25 mL) in a round bottomed flask (50 mL). The mixture was stirred at room temperature for a further 2 h and the reaction was quenched with water (20 mL). The organic components were extracted with ether (3 × 30 mL). The ether layers were removed, combined and dried over $MgSO_4$. The drying agent was filtered and the solvent was removed under reduced pressure. The crude product was weighed and then analysed by quantitative GC in the presence of tetradecane as added internal standard.

4.3 Typical experimental procedure for the chlorination of o-cresol and m-cresol

Freshly distilled sulfuryl chloride (4.66 mL, 57.7 mmol) was added slowly over 2 h to a mixture of *o*-cresol or *m*-cresol (5.41 g, 50 mmol), $AlCl_3$ (0.25 g, 1.875 mmol) and an additive (100 mg)

in a round bottomed flask (50 mL). The mixture was stirred at room temperature for a further 2 h, then worked-up and analyzed by GC as shown for *m*-xylenol.

4.4 Typical experimental procedure for the chlorination of phenol

Freshly distilled sulfuryl chloride (4.66 mL, 57.7 mmol) was added slowly over 2 h to a mixture of melted phenol (4.7 g, 50 mmol), $AlCl_3$ (50 mg, 0.375 mmol) and additive (50 mg) in a round bottomed flask (50 mL). The mixture was stirred at room temperature for a further 2 h then worked-up and analyzed by GC as shown for *m*-xylenol.

4.5 Computational methods

Calculations were carried out using Spartan '10 running on a Mac Pro computer at the B3LYP/6-31G* level of theory.

Disclosure statement

No potential conflict of interest was reported by the authors.

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