Regioselective chlorination of phenols in the presence of tetrahydrothiopyran derivatives

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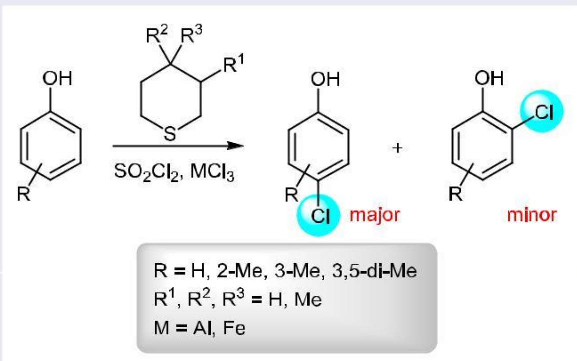
ABSTRACT
Four six-membered cyclic sulfides, namely tetrahydrothiopyran, 3-methyltetrahydrothiopyran, 4-methyltetrahydrothiopyran and 4,4-dimethyltetrahyrdrothiopyran have been used as moderators in chlorination reactions of various phenols with sulfuryl chloride in the presence of aluminum or ferric chloride. On chlorination of phenol, *ortho*-cresol and *meta*-cresol the *para/ortho* chlorination ratios and yields of the *para*-chloro isomers are higher than when no cyclic sulfide is used for all of the cyclic sulfides, but chlorination of *meta*-xylenol is less consistent, with some cyclic sulfides producing higher *p/o* ratios and others producing lower ratios than reactions having no sulfide present.



KEYWORDS
Chlorination; cyclic sulfides; *para/ortho* ratio; phenols; regioselectivity

1. Introduction

Several chlorinated phenols are employed as or used in the production of herbicides, pesticides, disinfectants, dyes, and pharmaceuticals [1,2]. For example, 2,4-dichlorophenol is an important intermediate in the production of commercial herbicides, while 4-chloro-3,5-dimethylphenol is used as a household antiseptic. Traditional phenol chlorination

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processes are not selective and produce significant waste [3]. Several chlorinating sys-tems have been reported for regioselective chlorination of phenols [4–16], including the use of Merrifield resin/sulfuryl chloride (SO_2Cl_2) [5], aluminum-pillared mont-morillonite clay or L type zeolites/SO_2Cl_2 [6], manganese(II) sulfate/hydrogen perox-ide/hydrogen chloride [7], ammonium chloride/1,3-dichloro-5,5-dimethylhydantoin [8], [*bis*(trifluoroacetoxy)iodo]benzene/aluminum chloride ($AlCl_3$) [9], and Nagasawa's *bis*-thiourea catalyst/*N*-chlorosuccinimide [10]. However, such chlorinating systems lead to either limited *para*-selectivity, or to high *ortho*-selectivity, or cannot be applied on a large scale. Therefore, development of *para*-selective chlorination processes is still needed.

Several sulfides have been used as selective catalysts for the production of *para*-chlorophenols [17–21]. For example, chlorination of phenol using SO_2Cl_2/diphenyl sulfide/$AlCl_3$ led to a *para*/*ortho* chlorophenol ratio of 10.5 [17]. Similarly, chlorination of *o*-cresol and *m*-cresol with such a system led to *para*/*ortho* ratios of 19.0 and 7.5, respectively [17]. The *para*-selectivity was attributed to the bulk of the active intermediate complex $Ph_2SCl^+AlCl_4^-$. Dialkyl sulfides (R–S–R') have also been used as selective mod-erators for production of *para*-chlorophenols. In this case, interesting variations were seen depending on the nature of the alkyl groups. In the absence of any Lewis acid, dibutyl and dipentyl sulfides showed greater *para*-selectivity for chlorination of phenol using sulfuryl chloride than other symmetrical dialkyl sulfides with either shorter or longer alkyl groups, and the *para*-selectivity was further enhanced in the presence of Lewis acids, especially $AlCl_3$ [18]. Also, with *m*-cresol as substrate, it was shown that the *para*-selectivity dropped as the level of steric hindrance of the alkyl group of alkyl *n*-butyl sulfides was increased from *n*-butyl to *tert*-butyl [18]. Clearly, these results are not consistent with the simple notion that the selectivity depends on the bulk of the complex $RR'SCl^+AlCl_4^-$.

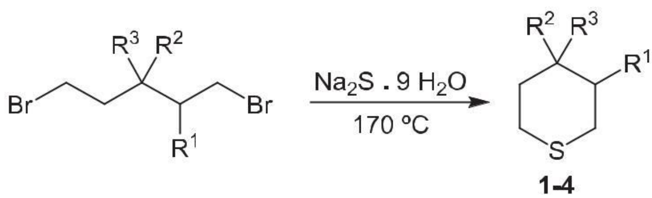
High *para*/*ortho* ratios have also been achieved in chlorination of phenols in the pres-ence of dithiaalkanes [R–S–$(CH_2)_n$–S–R]. In chlorination of *m*-cresol, compounds with longer spacer groups and with R groups around butyl in length provided the highest ratios (*para*/*ortho* ratio of 20.7 for $n = 12$ and R group *n*-butyl in the presence of $AlCl_3$) [19]. A more extensive study revealed that 1,ω-*bis*(methylthio)alkanes with longer spacer groups (ω = 6 or 9) showed greatest *para*-selectivity in chlorination of *m*-cresol (*para*/*ortho* ratio = 18.0) and *m*-xylenol (*para*/*ortho* ratio = 19.6), while 1,ω-*bis*(methylthio)alkanes with shorter spacer groups (ω = 2 or 3) showed greater *para*-selectivity in chlorination of phenol (*para*/*ortho* ratio = 11.4) and *o*-cresol (*para*/*ortho* ratio = 20.0) [20]. DFT calcu-lations suggested that dithiaalkanes with shorter and longer spacer groups adopt different intermediate structures, with short spacer intermediates involving a S–Cl^+–S arrangement of heteroatoms, while longer spacer intermediates involve a S–S^+–Cl arrangement. How-ever, use of disulfides as the moderators did not always follow the same pattern. For exam-ple, 1,2-dithiocane (hexamethylene disulfide) showed a higher *para*-selectivity (*para/ortho* ratio = 20.6) than 1,2-dithiolane (trimethylene disulfide) in chlorination of *o*-cresol, while 1,2-dithiolane was the more selective in *para*-chlorination of *m*-xylenol (*para/ortho* ratio = 19.1) [21]. On the other hand, *para*-selectivity in chlorination of both *o*-cresol and *m*-xylenol was higher with poly(trimethylene disulfide) than with poly(hexamethylene disulfide) [21]. Therefore, the factors influencing the levels of selectivity provided by different sulfur compounds as moderators are still unclear.

As part of our continuing contribution to the field of regioselective aromatic substi-tution reactions [22–39], in the current work we report the chlorination of a number of commercially important phenols using SO2Cl2 in presence of various tetrahydrothiopyran derivatives and a Lewis acid. The four tetrahydrothiopyrans chosen for the study were the parent tetrahydrothiopyran (**1**), 3-methyltetrahydrothiopyran (**2**), 4-methyltetrahydrothiopyran (**3**) and 4,4-dimethyltetrahydrothiopyran (**4**). Since earlier work had indicated that α-branching in the alkyl group of alkyl *n*-butyl sulfides caused significant diminution of the *para*-selectivity when used as the moderator in phenol chlo-rination reactions [18], 2-methyltetrahydrothiopyran was not included in the study. Com-pounds **2** and **3** offer alternative configurational/conformational arrangements between the active chlorine and the distal methyl group in the presumed chlorosulfonium inter-mediates, whereas compounds **1** and **4**, which will have different steric interactions at a distance from the active chlorine in the intermediate, would not show configurational differences. It was hoped, therefore, that some meaningful insight might be gained into the subtle effects that influence the selectivity induced by sulfur-containing activators in phenol chlorination reactions.

2. Results and discussion

The four tetrahydrothiopyrans **1–4** were synthesized by reactions of the appropriately sub-stituted 1,5-dibromopentanes with sodium sulfide nonahydrate at 170°C for 7 h (Scheme 1). The crude products obtained were purified by Kugelrohr distillation to give the pure cyclic sulfides **1−4** in 58–80% yield (Table 1) as colorless oils.

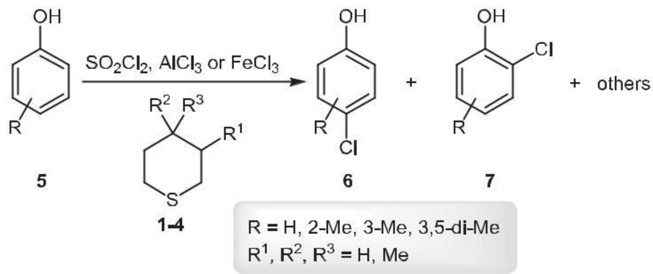
First, we attempted chlorination of phenol (**5**, R = H; 50 mmol) using freshly dis-tilled SO2Cl2 (55 mmol) in the presence of **1−4** (0.28 mmol) and AlCl 3 (50 mg) at room temperature (RT; Scheme 2). Also, the reaction was attempted in the absence of cyclic sulfides both with and without AlCl3 to provide a baseline. The results are presented in Table 2. Clearly, the presence of any one of the cyclic sulfides **1−4** led to production of 4-chlorophenol (**6**, R = H) in a better yield (83.2–89.0%) and with higher *para*-selectivity (*para*/*ortho* ratio = 12.7–18.2) than when no catalyst was used (yield 63.7–70.1% and



Scheme 1. Synthesis of tetrahydrothiopyrans **1−4**.

Table 1. Yields of tetrahydrothiopyrans **1−4** according to Scheme 1.

Sulfide	R^1	R^2	R^3	Yield (%)
1	H	H	H	80
2	Me	H	H	75
3	H	Me	H	79
4	H	Me	Me	58



Scheme 2. Chlorination of phenols in the presence of cyclic sulfides **1–4** and $AlCl_3$ or $FeCl_3$.

Table 2. Chlorination of phenol (**5**, R = H) according to Scheme 2.[a]

	Yield (%)[b]					
Sulfide	**5** (R = H)	**6** (R = H)	**7** (R = H)	Other	*p/o* ratio	Mass balance (%)[c]
—	10.7(8.2)	70.1 (63.7)	17.1 (21.1)	1.0 (0.7)[d]	4.1 (3.0)	98.8 (93.8)
1	5.8	89.0	5.0	—	17.8	99.8
2	10.8	83.2	5.6	—	14.7	99.6
3	2.3	88.1	6.9	—	12.7	97.3
4	6.7	87.8	4.8	—	18.2	99.3

[a]SO_2Cl_2 (4.44 ml, 55.0 mmol) was slowly added to a mixture of **5** (R = H; 4.71 g, 50.0 mmol), $AlCl_3$ (50 mg) and **1–4** (0.28 mmol) at RT over 2 h.

[b]Yield (%) based on quantitative GC and the yields in parentheses are for the reaction conducted without $AlCl_3$. [c]Total yield (%) for all identified products, as a check for losses due to unidentified materials.
[d]2,4-Dichlorophenol.

para/*ortho* ratio = 3.0–4.1). The unsubstituted tetrahydrothiopyran (**1**) led to the highest yield (89.0%) of 4-chlorophenol, while 4,4-dimethyltetrahyrdrothiopyran **4** provided the highest *para*/*ortho* ratio (18.2), but differences between the various moderators were not great and it is difficult to draw any general conclusions from such small differences, especially since significantly different quantities (2.3–10.8%) of unreacted phenol (**5**; R = H) were present in the different reaction mixtures.

Next, we investigated the chlorination of *o*-cresol (**5**, R = 2-Me; 50 mmol) under the same conditions that were used for phenol, in the absence and presence of cyclic sulfides (Scheme 2). The results obtained are recorded in Table 3. The yield of 4-chloro-2-methylphenol (**6**, R = 2-Me) was only 75.1% when the reaction was carried out in the presence of $AlCl_3$ without any of the cyclic sulfides **1–4**. In the presence of catalysts

Table 3. Chlorination of *o*-cresol (**5**, R = 2-Me) according to Scheme 2.[a]

	Yield (%)[b]				
Sulfide	**5** (R = 2-Me)	**6** (R = 2-Me)	**7** (R = 2-Me)	*p/o* ratio	Mass balance (%)[c]
—	9.6 (2.0)	75.1 (78.2)	11.9 (15.4)	7.8 (5.1)	99.0 (99.8)
1	—	96.4	2.1	45.7	98.5
2	4.6	93.6	2.3	40.0	100.5
3	—	96.6	2.4	40.4	99.0
4	4.0	90.0	2.7	33.2	96.7

[a]SO_2Cl_2 (4.44 ml, 55.0 mmol) was slowly added to a mixture of **5** (R = 2-Me; 5.41 g, 50.0 mmol), $AlCl_3$ (50 mg) and **1–4** (0.28 mmol) at RT over 2 h.
[b,c]See footnotes b and c to Table 1.

1−4, the yield of **6** (R = 2-Me) was very high (90.0–96.6%) and the *para*/*ortho* ratio was improved from 7.8, when no sulfide was used, to 33.2–45.7. Such results highlight the importance of the sulfur atom within the cyclic sulfides for the *para*-selectivity of the chlo-rination reaction. Tetrahydrothiopyran (**1**) was the most *para*-selective catalyst and led to the highest *para*/*ortho* ratio (45.7) and yield of **6** (96.4%). Again, however, the differences between the different cyclic sulfides were not great.

Chlorination of *m*-cresol (**5**, R = 3-Me; 50 mmol) with SO_2Cl_2 (55 mmol) and $AlCl_3$ gave the results recorded in Table 4. The yields of 4-chloro-3-methylphenol (**6**, R = 3-Me) obtained when cyclic sulfides were present were broadly comparable to that obtained when no sulfide was used (87.2%), but the *para*/*ortho* ratios were significantly increased from 9.2 in the absence of sulfide to 15.6–19.2 in the presence of **1–4** because the reaction mixtures contained significantly lower quantities of the *ortho*-isomer **7** (R = 3-Me) and significantly larger quantities of unreacted *m*-cresol (4.5–15.4%). 4,4-Dimethyltetrahydrothiopyran (**4**) provided the highest *para*/*ortho* ratio (19.2) and yield of **6** (R = 3-Me; 90.4%), although the differences with the different sulfides were again not large.

Finally, chlorination of *m*-xylenol (**5**, R = 2,3-di-Me; 50 mmol) was attempted under conditions similar to those used for the chlorination of other phenols. However, since *m*-xylenol is solid at RT and unlike the other phenols cannot be melted and then retain its liquid form in the presence of the other reaction components, a solvent (per-chloroethylene) had to be used. Also, $AlCl_3$ was replaced by ferric chloride ($FeCl_3$) as the activator, since in order to be consistent with the requirements for use of the prod-uct **6** (R = 2,3-di-Me) as a commercial household antiseptic the product would have to contain a very low proportion of Al. The results (Table 5) are in contrast with those obtained for other phenols. Cyclic sulfides **1** and **2** provided higher proportions of 4-chloro-3,5-dimethylphenol (*para*/*ortho* ratio = 9.0–13.5 compared with a *para*/*ortho* ratio of 6.9–7.0 when no sulfide was used), but sulfides **3** and **4** provided very low propor-tions of 4-chloro-3,5-dimethylphenol (*para*/*ortho* ratio = 1.9–3.7). Such results clearly indicate that steric hindrance within the moderator is not the only driving force for the regioselectivity of these reactions. Clearly, the sulfur atom within the cyclic sulfides has a significant effect on the regioselectivity of the chlorination reaction of phe-nols using SO_2Cl_2, but the wider structure of the sulfur-containing molecule is also important.

Table 4. Chlorination of *m*-cresol (**5**, R = 3-Me) according to Scheme 2.[a]

	Yield (%)[b]				
Sulfide	**5** (R = 3-Me)	**6** (R = 3-Me)[c]	**7** (R = 3-Me)	*p/o* ratio	Mass balance (%)[d]
—	2.5 (3.2)	87.2 (86.0)	9.5 (10.0)	9.2 (8.6)	99.2 (99.2)
1	4.3	89.6	5.7	15.6	99.6
2	7.9	82.9	5.2	15.9	96.0
3	15.4	78.4	4.5	17.3	98.3
4	4.7	90.4	4.7	19.2	99.8

[a]SO_2Cl_2 (4.44 ml, 55.0 mmol) was slowly added to a mixture of **5** (R = 3-Me; 5.41 g, 50.0 mmol), $AlCl_3$ (0.25 g) and **1−4** (0.40 mmol) at RT over 2 h.

[b]See footnote b to Table 1.

[c]Sum total of mixture of 2-chloro-3-methylphenol and 6-chloro-3-methylphenol (the two *ortho*-chlorinated products), which were not fully resolved by the GC system used.

[d] See footnote c to Table 1.

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Table 5. Chlorination of *m*-xylenol (**5**, R = 3,5-di-Me) according to Scheme 2.[a]

Sulfide	Yield (%)[b] **5** (R = 3,5-di-Me)	**6** (R = 3,5-di-Me)	**7** (R = 3,5-di-Me)	Other[d]	*p/o* ratio	Mass balance (%)[c]
—	15.4 (13.4)	71.1 (68.6)	10.3 (9.8)	— (—)	6.9 (7.0)	96.8 (91.8)
1	2.8	89.1	6.6	0.7	13.5	99.2
2	7.1	78.1	8.7	2.9	9.0	96.8
3	15.4	53.8	27.7	—	1.9	96.9
4	5.8	73.6	19.7	—	3.7	99.1

[a]SO_2Cl_2 (4.44 ml, 55.0 mmol) was slowly added to a mixture of **6** (R = 3,5-di-Me; 6.11 g, 50.0 mmol), $FeCl_3$ (25 mg) and **1–4** (0.05 mmol) in tetrachloroethylene (TCE; 25 ml) at RT over 2 h.

bYield (%) based on quantitative GC and the yields in parentheses are for the reaction conducted without $FeCl_3$. [c]See footnote c to Table 1.

[d]2,4-Dichloro-3,5-dimethylphenol.

3. Conclusion

Four cyclic sulfides have been synthesized and used as potential moderators for chlorination of phenols with freshly distilled sulfuryl chloride and a Lewis acid promoter. For three of the phenols tested (phenol, *ortho*-cresol and *meta*-cresol) the *para*-isomers were produced more regioselectively and usually in (often substantially) higher yields than in corresponding reactions carried out in the absence of cyclic sulfide, regardless of the cyclic sulfide used. However, the situation with *meta*-xylenol was different, with two of the sulfides (**1** and **2**) giving an increased proportion of *para*-chlorinated product and two (**3** and **4**) giving a higher proportion of *ortho*-chlorinated product than in the absence of any sulfide. Since the methyl group(s) in these latter sulfides are further away from the active sulfur atom than the methyl group in **2** it does not appear that the only driving force for the selectivity changes is steric hindrance, providing further support for the idea that the effects of sulfur compounds on such chlorination reactions are more subtle.

4. Experimental Section

4.1. General

Chemicals purchased from Aldrich and Lancaster Chemicals were mostly used as purchased. Sulfuryl chloride was distilled under an inert atmosphere at atmospheric pressure. Gas chromatography (GC) was carried out using a Shimadzu GC-2014 instrument with a capillary ZB Carbowax column (30 m, 0.32 mm ID) and temperature programed (40°C for 3 min, then ramped at 10°C/min to 220°C, then held for 8 min) with an injection tempera-ture of 300°C and a detection temperature 250°C. To allow quantification, tetradecane was added as a standard. Commercial samples of expected phenol chlorination products were used to determine retention times and response factors for each product. ^1H (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded on a Bruker AV400 spectrometer. Chemi-cal shifts δ are reported in parts per million (ppm) relative to TMS and coupling constants J in Hz have been rounded to the nearest integer. DEPT spectra were used to determine ^{13}C multiplicities. Assignments of NMR signals are based on expected chemical shifts, integration values and coupling patterns and have not been rigorously confirmed. Low-resolution mass spectra were recorded on a Quattro II spectrometer at 70 eV. High-resolution mass spectra data were obtained on a MAT900 instrument.

4.2. Typical procedure for the preparation of cyclic sulfides 1−4

A mixture of the appropriately substituted 1,5-dibromopentane and sodium sulfide non-ahydrate (for quantities, see individual compound sections) was heated at 170°C for 7 h in an oil bath. After cooling, water (20 ml) and dichloromethane (DCM, 20 ml) were added. The phases were separated and the aqueous layer was re-extracted with DCM (3 × 20 ml). The combined organic phases were washed with H_2O (30 ml) and dried over anhydrous $MgSO_4$. Removal of the solvent under reduced pressure gave the crude product, which was purified by Kugelrohr distillation to give the pure cyclic sulfides **1−4**.

4.2.1. Tetrahydrothiopyran (1)

Yield 1.60 g (80%) from 1,5-dibromopentane (4.00 g, 17.4 mmol) and sodium sulfide non-ahydrate (6.27 g, 26.1 mmol) as a colorless oil (Bp 50−55°C at 15 mmHg; lit. 140−141°C at RT [40]). ^{1}H-NMR ($CDCl_3$) δ (ppm): 1.60 (m, 2 H), 1.85 (m, 4 H), 2.65 (m, 4 H); ^{13}C-NMR ($CDCl_3$) δ (ppm): 26.8, 28.1, 29.4; MS- EI$^+$ m/z (%) 102 ([M]$^+$, 100), 87 (95), 67 (60), 46 (75), 39 (80).

4.2.2. 3-Methyltetrahydrothiopyran (2)

Yield 1.44 g (75%) from 1,5-dibromo-2-methylpentane (4.01 g, 16.4 mmol) and sodium sulfide nonahydrate (7.88 g, 32.8 mmol) as a colorless oil (Bp 70°C at 20 mmHg; lit. 158°C at RT [41]). ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.89 (d, J = 7.5 Hz, 3 H), 1.61−2.00 (m, 5 H), 2.22−2.53 (m, 4 H); ^{13}C-NMR ($CDCl_3$) δ (ppm): 23.1, 28.1, 28.8, 33.5, 35.2, 36.1; MS EI$^+$ m/z (%) 116 ([M$^+$] 90), 101 (100).

4.2.3. 4-Methyltetrahydrothiopyran (3)

Yield 0.38 g (79%) from 1,5-dibromo-3-methylpentane (1.00 g, 4.1 mmol) and sodium sul-fide nonahydrate (1.48 g, 6.1 mmol) as a colorless oil (Bp 50−55°C at 20 mmHg; lit. 54°C at 22 mmHg [41]). ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.85 (d, J = 6 Hz, 3 H), 1.10 −1.40 (m, 4 H), 1.90 (m, 1 H), 2.45−2.55 (m, 4 H). ^{13}C-NMR ($CDCl_3$) δ 23.4, 29.2, 32.6, 36.3; MS EI m/z (%) 116 ([M]$^+$, 100), 101 (95), 67 (90), 41 (85).

4.2.4. 4,4-Dimethyltetrahyrdrothiopyran (4)

Yield 0.26 g (58%) from 1,5-dibromo-3,3-dimethylpentane (1.00 g, 3.87 mmol) and sodium sulfide nonahydrate (1.40 g, 5.81 mmol) as a colorless oil (Bp 60−65°C at 15 mmHg; lit. 57−58°C at 15 mmHg [42]). ^{1}H-NMR ($CDCl_3$) δ (ppm): 0.75 (s, 6 H), 1.40−1.60 (m, 4 H) 2.50−2.60 (m, 4 H); ^{13}C-NMR ($CDCl_3$) δ (ppm): 24.8, 26.9, 28.8, 40.2; MS EI$^+$ m/z (%) 130 ([M]$^+$, 90), 115 (95), 69 (70), 41 (80).

4.3. Chlorination of phenol, o-cresol and m-cresol

Phenol (melted), *o*-cresol (melted) or *m*-cresol (50.0 mmol), $AlCl_3$ (25−50 mg) and the appropriate cyclic sulfide **1−4** (0.28−0.40 mmol; see Tables 1–4 for details) were placed in a dried round bottomed flask (50 ml). The mixture was stirred as sulfuryl chloride (4.44 ml, 55.0 mmol) was added slowly over 2 h *via* a pressure equalizing dropping funnel and for 2 h further. The reaction was quenched with water (20 ml) and the organic components were then extracted with diethyl ether (3 × 30 ml). The combined ether layers were dried over

$MgSO_4$, which was removed by filtration. The solvent was removed under reduced pressure to give the crude product, which was weighed. Quantitative GC analysis was conducted on a weighed aliquot of the product with a known quantity of tetradecane.

4.4. Chlorination of m-xylenol

m-Xylenol (6.11 g, 50.0 mmol), $FeCl_3$ (25 mg), tetrachloroethylene (25 ml) and the appro-priate cyclic sulfide **1–4** (0.05 mmol) were placed in a dried round bottom flask (50 ml). The mixture was stirred as freshly distilled sulfuryl chloride (4.44 ml, 55.0 mmol) was added slowly over 2 h *via* a pressure equalizing dropping funnel and then for another 2 h. The work-up and analysis of the products by GC were as previously described for other phenols.

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Disclosure statement

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