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Review

Development of Efficient and Selective Processes for the Synthesis of Commercially Important Chlorinated Phenols

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Abstract: *para*-Selective processes for the chlorination of phenols using sulphuryl chloride in the presence of various sulphur-containing catalysts have been successfully developed. Several chlorinated phenols, especially those derived by *para*-chlorination of phenol, *ortho*-cresol, *meta*-cresol, and *meta*-xylenol, are of significant commercial importance, but chlorination reactions of such phenols are not always as regioselective as would be desirable. We, therefore, undertook the challenge of developing suitable catalysts that might promote greater regioselectivity under conditions that might still be applicable for the commercial manufacture of products on a large scale. In this review, we chart our progress in this endeavour from early studies involving inorganic solids as potential catalysts, through the use of simple dialkyl sulphides, which were effective but unsuitable for commercial application, and through a variety of other types of sulphur compounds, to the eventual identification of particular poly(alkylene sulphide)s as very useful catalysts. When used in conjunction with a Lewis acid such as aluminium or ferric chloride as an activator, and with sulphuryl chloride as the reagent, quantitative yields of chlorophenols can be obtained with very high regioselectivity in the presence of tiny amounts of the polymeric sulphides, usually in solvent-free conditions (unless the phenol starting material is solid at temperatures even above about 50 °C). Notably, poly(alkylene sulphide)s containing longer spacer groups are particularly *para*-selective in the chlorination of *m*-cresol and *m*-xylenol, while, ones with shorter spacers are particularly *para*-selective in the chlorination of phenol, 2-chlorophenol, and *o*-cresol. Such chlorination processes result in some of the highest *para*/*ortho* ratios reported for the chlorination of phenols.

Keywords: selective chlorination; phenols; sulphuryl chloride; sulphur-containing catalysts; aromatic electrophilic substitution reactions; monochlorination; double chlorination; *para*/*ortho*-isomer ratio

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1. Introduction

Phenols are used as intermediates in the production of a variety of valuable industrial products such as pharmaceuticals (e.g., aspirin) [1], explosives [2], picric acid [3], azo dyes [4], antioxidants [5], plastics [6], and disinfectants [7]. In this review, we are particularly concerned with commercially important chlorophenols, especially those derived by *para*-chlorination of those phenols that can be obtained in bulk from the distillation of crude petroleum or coal tar, notably phenol, *o*-cresol, *m*-cresol, and *m*-xylenol. Such chlorination reactions generally produce mixtures of *ortho*- and *para*-substituted phenols [8]. However, in these environmentally conscious times, it is important to enhance the proportion of the commercially desirable material in an economically realistic manner, and that has been the purpose of our work in this area.

1.1. Commercial Importance of Chlorinated Phenols

Chlorinated phenols and in particular 4-chloro isomers are useful intermediates in organic syntheses or as end products themselves. They are produced on an industrial scale

and used in the production of antiseptics, herbicides, pesticides, and dyes [9]. For example, 2,4-dichlorophenoxyacetic acid and 2,4,5-trichlorophenoxyacetic acid act as herbicides [10], 2,4,5-trichlorophenol acts as a leather and wood fungicide [11], 2,3,4,5,6-pentachlorophenol is used as an insecticide [12], and 4-chloro-3,5-dimethylphenol is used as a household and hospital disinfectant [13–15]. Figure 1 shows some of the most common industrial products containing chlorinated phenolic components.

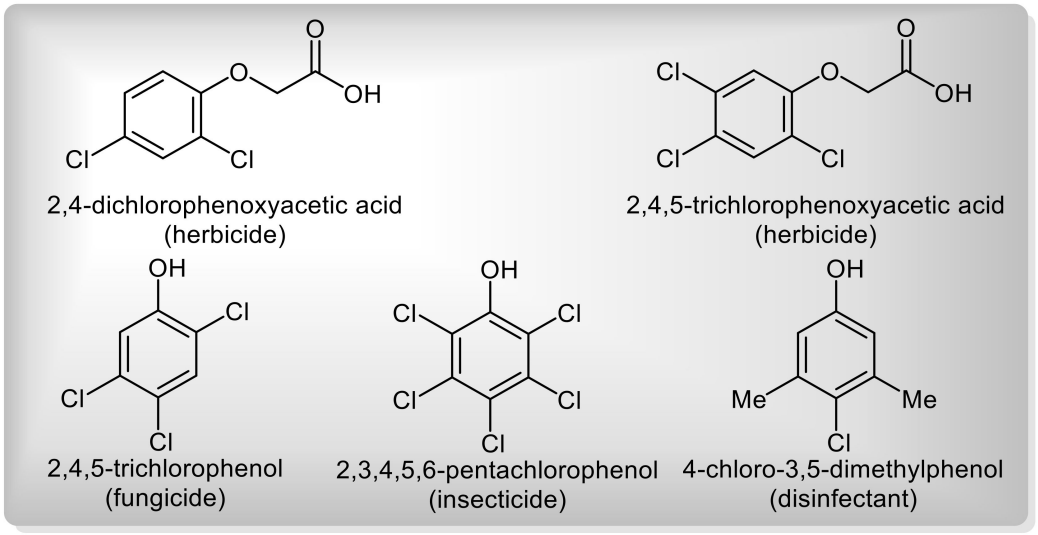


Figure 1. Common industrial products containing chlorinated phenols.

1.2. Research Group Background in Selective Aromatic Substitution Reactions

Our research group has developed many processes for the production of valuable materials through regioselective aromatic substitution reactions over reusable solids such as zeolites [16–19]. The procedures allowed the production of *para*- or linear isomers in high yields in alkylation [20,21], acylation [22,23], methanesulphonylation [24], and nitration [25–31] of aromatic compounds. For example, remarkable regioselectivity was achieved in dialkylation of naphthalene with *tert*-butyl alcohol in cyclohexane over zeolite H-mordenite to produce 2,6-di-*tert*-butylnaphthalene in high yield (60%), along with 2,7-di-*tert*-butylnaphthalene and 2-*tert*-butylnaphthalene in 1% and 10% yields, respectively [21] and pure 2,6-di-*tert*-butylnaphthalene could be crystallised directly from the product mixture.

Of particular significance in the context of this review is that we have also studied halogenation of various aromatic compounds over structured solids, and this was the starting point for our investigation of selective chlorination of phenols.

2. The Use of Structured Solids to Influence the Halogenation Reactions of Aromatic Compounds

Our earliest attempts at controlling halogenation reactions of aromatic compounds by use of solid additives involved the use of silica [32–37]. For example, the chlorination of various monosubstituted benzenes using *tert*-butyl hypochlorite over silica resulted in the corresponding *ortho*- and *para*-disubstituted benzenes. However, the process was not very selective towards the *para*-isomers. The highest *para*/*ortho* ratios were obtained in chlorination of *tert*-butylbenzene (85/15) and anisole (70/30) in tetrachloromethane (CCl_4) at 25 °C [32], but the regioselectivity was not very different from that in traditional chlorination reactions of such substrates. Successful regioselective bromination of indoles, benzimidazoles, β-carbolines, and iminodibenzyls was achieved using *N*-bromosuccinimide over silica. Such reactions provided high yields of the corresponding bromo derivatives, often quite regioselectively, but again the regioselectivity was largely dependent on the nature of the substrate [33,34].

The use of zeolites rather than silica led to much higher *para*-selectivity in halogenation reactions of simple aromatics [38–41]. For example, bromination of toluene using *tert*-butyl hypobromite over zeolite NaX (13X molecular sieve) in a mixture of diethyl ether and CCl_4 (3:1 by volume) produced 4-bromotoluene selectively, but in moderate yield (49%) [40]. The use of bromine over zeolite NaY in dichloromethane (DCM) produced 4-bromotoluene in 98% yield, along with 2-bromotoluene in 1% yield [41]. Such *para*-regioselectivity appears to be the highest achieved to date for direct bromination of toluene and the reaction has been adapted as an undergraduate laboratory experiment [42]. The optimal system for *para*-selective chlorination of toluene involved the use of *tert*-butyl hypochlorite in acetonitrile over zeolite HX [38].

3. Early Studies of Halogenation of Phenols

Since the use of solids in substitution reactions of aromatic compounds had in some cases led to significant enhancement in *para*-selectivity, we hoped that the halogenation of phenols could be controlled in similar ways. As phenols are substantially more reactive towards electrophilic substitution than most other kinds of aromatic compounds, in order for the intrinsic rate of reaction to be slow enough to allow a solid to influence its course, quite mild halogenating agents were required and *N*-chlorodialkylamines were chosen for chlorination reactions. However, chlorination of phenols using *N*-chlorodialkylamines over silica was not selective towards *para*-chlorophenols. Instead, a high *ortho*/*para* ratio of chlorinated phenols was achieved, depending on the phenol [43]. The *ortho*/*para* ratio was 15.8 for phenol, 8.2 for *o*-cresol, and 4.7 for 2-chlorophenol when *N*-chloro-*bis*(2-chloroethyl)amine was used over silica. Although the results were interesting and provided good *ortho*-selectivity, the approach was clearly not going to be appropriate for the production of the important commercial *para*-chlorophenols. In addition, the use of zeolites, which had been so successful in promoting *para*-nitration of toluene and other aromatic substrates [30,31], when applied to nitration reactions of phenol using a mild nitration agent, *iso*-propyl nitrate, resulted in 2-nitrophenol rather than 4-nitrophenol as the major product (*ortho*/*para* ratio = 2–3) [44], suggesting that phenols were less amenable to the same sorts of considerations as less reactive aromatic substrates. Nevertheless, the Sheldon group showed that chlorination of phenol using SO_2Cl_2 in the presence of a large quantity (10 g for 100 mmol of phenol) of partially cation-exchanged L-type zeolite (H^+, Na^+, K^+, and Al^{3+}) in 2,2,4-trimethylpentane as a solvent at room temperature could provide 4-chlorophenol in 85% yield and a *para*/*ortho* ratio of 8 [45], which are higher than obtained by direct chlorination of phenol with sulphuryl chloride in solvent-free conditions (ca. 75% yield, *para*/*ortho* ratio ca. 3.4). However, the advantage of higher yield is unlikely to outweigh the disadvantages of the procedure for commercial-scale application. The use of montmorillonite clay (10 g for 100 mmol of phenol) under similar reaction conditions gave 4-chlorophenol in even lower yield (76%) and selectivity (*para*/*ortho* = 5.7) than the use of the zeolite [45].

Quaternary ammonium tribromides are mild brominating agents and we felt that the use of a polymeric example might allow recovery and reuse of the corresponding polymeric quaternary ammonium bromide after reaction; thus, we undertook studies of the bromination of various phenols (phenol, 2-chlorophenol, *o*-cresol, *m*-cresol, and guaiacol) using the tribromide derivative of Amberlyst-A26 (a macroreticular resin with quaternary ammonium functionality) [46]. Indeed, the reaction proved to be successful and was highly selective towards the *para*-isomers, but the process is not likely to be attractive on a bulk commercial scale and, in any case, has no counterpart for chlorination reactions. Therefore, we concluded that a totally different approach was required in order to develop a commercially attractive route to *para*-chlorophenols.

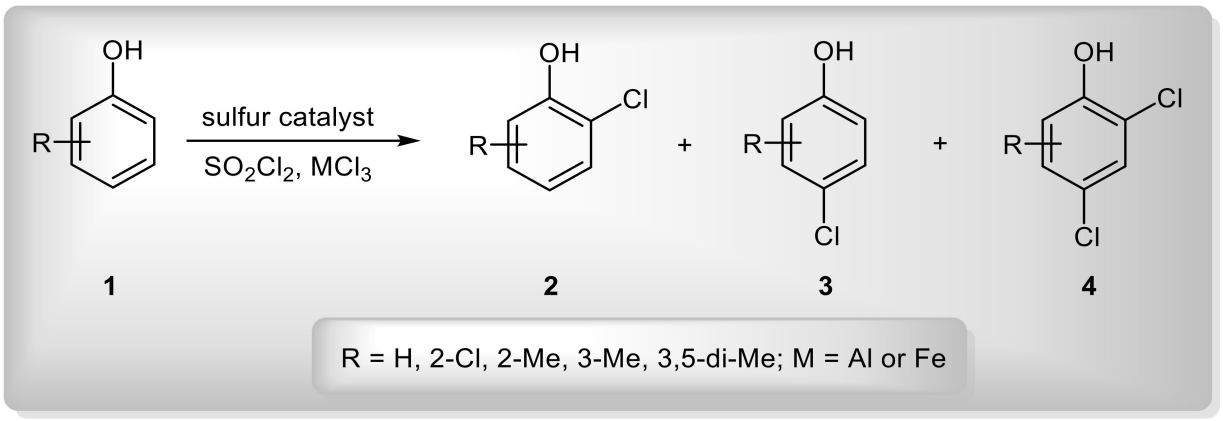
4. Development of a Successful Approach to *para*-Chlorination of Phenols Using Sulphur Compounds as Catalysts

Many other approaches have been attempted for the chlorination of phenols; however, the processes have generally not been highly selective towards the *para*-isomers [47–52].

Various chlorinating agents have been used, but sulphuryl chloride (SO_2Cl_2) seems to be the most promising for the formation of *para*-isomers [52–59]. The use of Merrifield resin in three-step chlorination of *o*-cresol led to an excellent *para/ortho* ratio of 50 [53], but the process involved a coupling step in which *o*-cresol was bound to the resin in the presence of caesium carbonate and sodium iodide in dimethylformamide over 24 h, followed by chlorination of the resin-bound *o*-cresol, and then decoupling of the chlorocresol from the resin using trifluoroacetic acid in dichloromethane (DCM). In addition, the process was applied only on a 0.33 mmol scale. Such a procedure would not be applicable on an industrial scale. Sulphur-containing catalysts such as diphenyl sulphide (Ph_2S) had provided quite good *para/ortho* ratios in the chlorination of phenols. For example, the use of SO_2Cl_2 and Ph_2S in the presence of aluminium chloride ($AlCl_3$) led to a *para/ortho* ratio of around 20 for the chlorination products of *o*-cresol [54–56]. Additionally, chlorodimethylsulphonium chloride had been used for the chlorination of phenols [59]. Therefore, we considered that further investigation of the use of sulphur compounds might be an appropriate way forward for the development of highly selective chlorination processes with minimal environmental impact. Details of our studies are reported below.

4.1. Results with Simple Dialkyl Sulphides and Some Cyclic Analogues

The speculation in early reports of the use of sulphur compounds in presence of Lewis acids such as aluminium chloride as catalysts for chlorination of phenols had been that the better *para*-selectivity achieved was due to the hindered nature of the active chlorinating agent, believed to be a chlorosulphonium tetrachloroaluminate (R_2SCl^+ $AlCl_4^-$). Our first investigation was therefore to check how chain length and chain branching in dialkyl sulphides affected the selectivity. We decided to test chlorination of phenol (**1**; R = H, Scheme 1) and *m*-cresol (**1**; R = 3-Me) in the presence of a range of such sulphur-containing catalysts (Figure 2) and $AlCl_3$ using SO_2Cl_2 (110 mmol for 100 mmol of **1**). Some representative results are given in Table 1 [60,61].



Scheme 1. Chlorination of phenols (**1**) using SO_2Cl_2 over sulphur-containing catalysts.

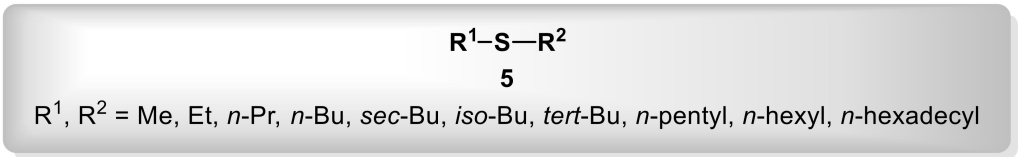


Figure 2. Structures of dialkyl sulphides **5** used in the study.

Table 1. Effect of dialkyl sulphides **5** (R^1SR^2) on the selectivity of chlorination of phenols according to Scheme 1 [a].

Entry	Substrate	R^1	R^2	R^1R^2S (mmol)	$AlCl_3$ (mmol)	Temperature (°C)	3:2 Ratio [b]
1	Phenol	—	—	—	—	35	4.8
2	Phenol	Me	Me	2.7	—	20	2.4
3	Phenol	*n*-Bu	*n*-Bu	2.7	—	20	9.7
4	Phenol	*n*-hexyl	*n*-hexyl	2.7	—	20	7.7
5	*m*-Cresol	—	—	—	—	20	8.9
6	*m*-Cresol	*n*-Bu	*n*-Bu	2.7	—	20	12.1
7	*m*-Cresol	*n*-Bu	*n*-Bu	2.7	3.8	20	17.3
8	*m*-Cresol	*n*-Bu	*iso*-Bu	2.7	3.8	20	17.2
9	*m*-Cresol	*n*-Bu	*sec*-Bu	2.7	3.8	20	17.1
10	*m*-Cresol	*n*-Bu	*tert*-Bu	2.7	3.8	20	8.7

[a] Conditions: 100 mmol substrate, 110 mmol SO_2Cl_2, 4 h at the stated temperature. [b] In the case of *m*-cresol, the *ortho* product **2** is a mixture of 2-chloro-3-methylphenol (minor) and 6-chloro-3-methylphenol (major).

Preliminary tests had revealed that around 2.7 mmol of dialkyl sulphides **5** and 3.8 mmol of aluminium chloride were sufficient to produce a significant effect on selectivity. In the absence of any additive, it was necessary to maintain a temperature of 35 °C in order for neat phenol to remain liquid, but in the presence of additives, molten phenol remained liquid after cooling to room temperature, and reactions were conducted at 20 °C. In the case of *meta*-cresol, which is liquid at 20 °C, this was not an issue. As can be seen from Entries 2–4 in Table 1, the presence of dialkyl sulphides **5** significantly influenced the regioselectivity of chlorination of phenol even without the presence of aluminium chloride, but the degree of *para*-selectivity increased when aluminium chloride was also present (ratio **2**:**3** = 15.7 for phenol in presence of *n*-Bu_2S [62]; compare also Entries 6 and 7 for chlorination of *m*-cresol, for example). The length of the alkyl chains of the dialkyl sulphides had a marked effect on the selectivity; *para*-selectivity indeed increased as the chain length increased from methyl to butyl, which resulted in the maximum selectivity (dipropyl and dipentyl sulphides were only marginally poorer than dibutyl sulphide), but longer chains resulted in the selectivity dropping again. Assuming simple steric hindrance was responsible for improving the selectivity, we surmised that in the highly polar liquid phenolic environment, longer alkyl chains might wrap around on themselves to create a protective layer around the sulphur atom, thereby limiting its ability to influence the course of the reaction.

Replacing one of the *n*-Bu groups of dibutyl sulphide by more hindered isomeric butyl groups (see Entries 7–10, Table 1) had little impact on the selectivity except with the most hindered *tert*-butyl, which resulted in a significant ***lowering*** of the *para*-selectivity. This last result was clearly not in line with a simple notion that increased hindrance causes greater *para*-selectivity, but we surmised that the level of hindrance, in this case, might be so great that approach of the dialkylchlorosulphonium tetrachloroaluminate to the substrate might be inhibited, thereby limiting its influence over the reaction and allowing a larger proportion of the reaction to proceed through direct reaction with sulphuryl chloride. Di-*iso*-propyl sulphide, however, was similar to di-*n*-butyl sulphide in its ability to provide a high yield of *para*-chlorinated product with great selectivity [62].

Use of the cyclic dialkyl sulphides tetrahydrothiopyran and some methyl-substituted tetrahydrothiopyrans (**6**–**9**; Figure 3) produced similar results to dibutyl sulphide in reactions with phenol and *m*-cresol, and we showed that smaller quantities of both the dialkyl sulphide (0.28 mmol for 50 mmol of **1**) and aluminium chloride (25–50 mg for 50 mmol of **1**) could be used to gain similar levels of selectivity [63]. Under similar reaction conditions, the chlorination of *o*-cresol (**1**; R = 2-Me), which has only one *ortho*-position available for chlorination, was very selective towards the *para*-isomer **3** (R = 2-Me) with all of the tetrahydrothiopyrans **6**–**9**, with the highest selectivity being achieved over unsubstituted tetrahydrothiopyran **6** (96% yield; *para*/*ortho* ratio = 45.7) [63]. Additional difficulties arise with *m*-xylenol, which melts at a higher temperature, thereby requiring a solvent for re-

actions at the modest temperatures used for the other phenols, and where there is a limit with respect to the concentration of aluminium for the commercially important product, 4-chloro-*m*-xylenol. Therefore, reactions were conducted in the presence of $FeCl_3$ (25 mg) in tetrachloroethylene (25 mL). Tetrahydrothiopyran **6** again provided the highest yield of **3** (R = 3,5-di-Me; 89.1%) with a *para/ortho* ratio of 13.5 on chlorination of *m*-xylenol (**1**; R = 3,5-di-Me) under these conditions [63].

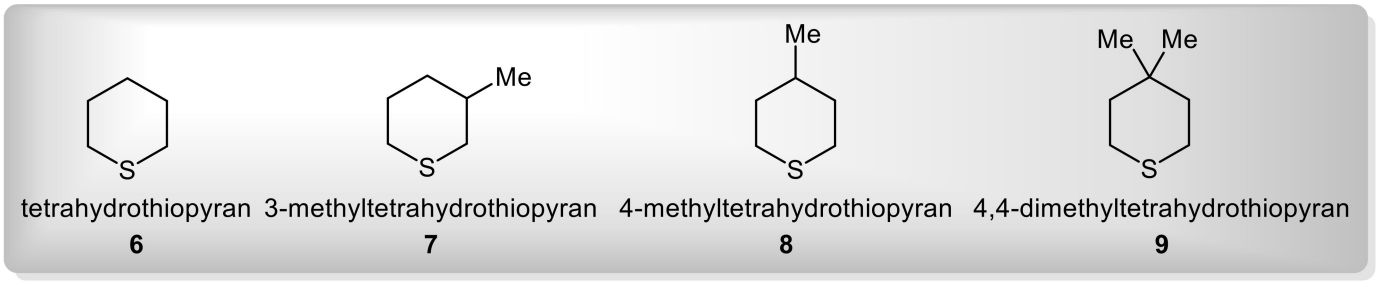


Figure 3. Structures of tetrahydrothiopyrans **6**–**9** used in the study.

We also tested some other simple sulphur compounds, such as sulphoxides and sulphones, as potential catalysts [62], but did not find any that were as good as the simple sulphides, especially dibutyl sulphide, di-*iso*-propyl sulphide, and tetrahydrothiopyran. These simple sulphides had indeed provided exceptional selectivity, and we scaled up a reaction with *m*-cresol sevenfold with di-*iso*-propyl sulphide as the catalyst and showed that the results could be reproduced at the greater scale [62]. The di-*iso*-propyl sulphide catalyst could be recovered by distillation, but unfortunately, it was difficult to remove the last traces of odour of the sulphur compound from the chlorocresol product, and there was also a concern that if such a process were to be introduced commercially, it would cause problems in the locality of the production site as a result of the stench from even a small escape of the catalyst into the environment. Therefore, we decided to try to find ways around the issue and considered the use of larger molecules containing more than one sulphur atom to be a useful approach. Our initial studies were with dithiaalkanes.

4.2. Results with Dithiaalkanes ***10*** *[$(H(CH_2)_mS(CH_2)_nS(CH_2)_mH$] and Related Compounds*

Our first thoughts were that less volatile dithiaalkanes might be suitable for providing high selectivity without some of the disadvantages of the more volatile dialkyl sulphides. We undertook a study of a range of dithiaalkanes (**10**; Figure 4) as catalysts in the chlorination of *m*-cresol (**1**; R = 3-Me) under reaction conditions similar to those used previously with simple dialkyl sulphides [64,65]. The results (a selection is provided in Figure 5) showed that to a first approximation the selectivity increased with the length of the spacer group between the two sulphur atoms (see charts A and B) and that the optimal terminal alkyl group length was around 3–5 carbon atoms long (see chart C). The best result was achieved over 5,18-dithiadocosane ($BuSC_{12}H_{24}SBu$), which produced 4-chloro-*m*-cresol (**3**; R = 3-Me) in 91.8% absolute yield and a *para/ortho* ratio of 20.7 when used in conjunction with aluminium chloride.

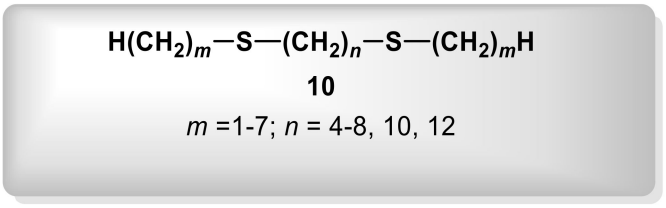


Figure 4. Structures of dithiaalkanes **10** used in the study.

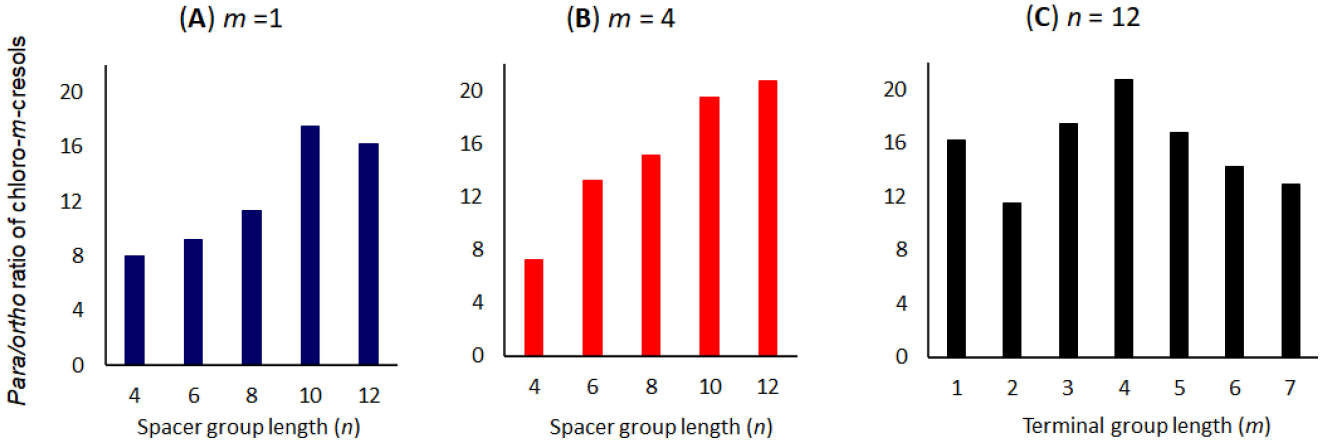


Figure 5. Effect of variation of terminal and spacer group length of dithiaalkanes **10** [$(H(CH_2)_mS(CH_2)_nS(CH_2)_mH$] on the selectivity of chlorination of *m*-cresol (**1**, R = 3-Me) according to Scheme 1. Conditions: *m*-cresol (100 mmol), SO_2Cl_2 (110 mmol), dithiaalkane (2.7 mmol), $AlCl_3$ (3.8 mmol), 20 °C, 4 h. The *ortho*-product **2** (R = 3-Me) is a mixture of 2-chloro-3-methylphenol (minor) and 6-chloro-3-methylphenol (major). Some of the results have not been previously published [62]. (**A**) Terminal groups are Me; spacer length varied; (**B**) Terminal groups are *n*-Bu; spacer length varied; (**C**) Spacer group is twelve CH_2 groups long; terminal group length varied.

Although this catalyst provided excellent yield and selectivity for chlorination of *m*-cresol and overcame the problems of odour and volatility associated with the simple dialkyl sulphides, it did not perform equally well with all of the other target phenols. Preliminary results with *o*-cresol, for example, suggested that dithiaalkanes with shorter spacer groups between the sulphur atoms provided greater *para*-selectivity than 5,18-dithiadocosane. This suggested again that the improved *para*-selectivity experienced on chlorination of phenolic compounds in the presence of sulphur-containing catalysts was not simply the result of the increased bulk of the active chlorinating agent but was also influenced by more subtle factors.

One possibility to explain some of the variations in the case of dithiaalkanes was some kind of interaction between the most polar region of the phenol (the OH group) and one of the sulphur atoms of the dithiaalkane, resulting in the other sulphur atom, which might be the one that became part of the active chlorinating agent, favouring particular areas of space dependent on the length of the spacer group and the location of any other encumbering features, such as substituents on the phenolic ring. In order to investigate such a possibility, we decided to study the effect of replacing one of the alkylthio groups of dithiaalkanes by more polar groups, in particular OH or methoxy groups, which might be expected to experience a stronger interaction with the OH group of the phenol and therefore a more pronounced influence over the selectivity.

We synthesised a range of ω-hydroxy-1-(methylthio)alkanes **11**, ω-methoxy-1-(methyl thio)alkanes **12**, and 1,ω-*bis*(methylthio)alkanes **13** (Figure 6) and tested them in chlorination reactions of the four phenols of interest (**1**,R = H, 2-Me, 3-Me and 3,5-di-Me, Scheme 1). For pragmatic reasons, the reaction conditions for the different phenols were somewhat different, and because of limited supplies of the synthesised catalysts, it was convenient to use a constant mass of catalyst rather than a constant molar amount within the series for any one phenol, but it was expected that the trends observed would nevertheless be informative. The results are shown in Figure 7 [66].

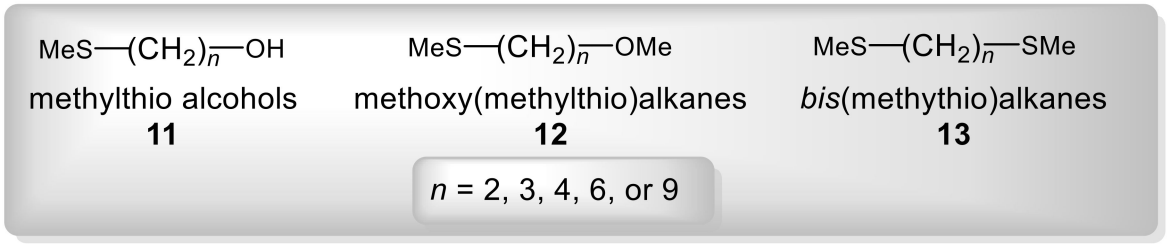


Figure 6. Structures of ω-substituted-1-(methylthio)alkanes **11–13** used in the study.

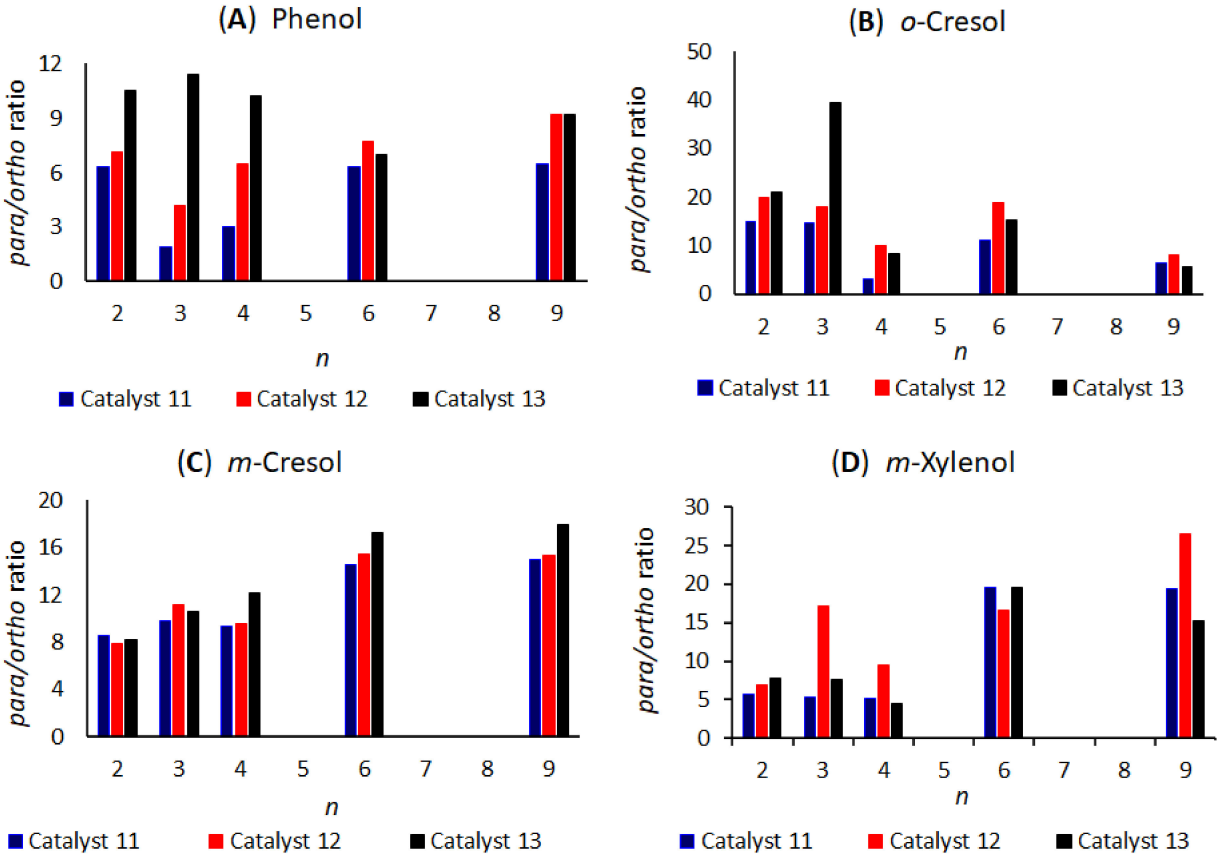


Figure 7. Effect of ω-substituted-1-(methylthio)alkanes [$MeS(CH_2)_nX$] **11–13** on the selectivity of chlorination of phenols according to Scheme 1. Conditions: For phenol (Chart **A**): 50 mmol substrate, 57.7 mmol SO_2Cl_2, 50 mg $AlCl_3$, 50 mg sulphur compound, 2 h addition of SO_2Cl_2 then 2 h at room temperature. For *o*-cresol (Chart **B**): 50 mmol substrate, 57.7 mmol SO_2Cl_2, 250 mg $AlCl_3$, 100 mg sulphur compound, 2 h addition of SO_2Cl_2 then 2 h at room temperature. For *m*-cresol (Chart **C**): 50 mmol substrate, 57.7 mmol SO_2Cl_2, 250 mg $AlCl_3$, 100 mg sulphur compound, 2 h addition of SO_2Cl_2 then 2 h at room temperature. For *m*-xylenol (Chart **D**): 50 mmol substrate, 57.7 mmol SO_2Cl_2, 25 mg $FeCl_3$, 30 mg sulphur compound, 25 mL dichloromethane (DCM), 2 h addition of SO_2Cl_2 then 2 h at room temperature. In the case of *m*-cresol, the *ortho*-product **2** is a mixture of 2-chloro-3-methylphenol (minor) and 6-chloro-3-methylphenol (major).

It should be noted that for large *para/ortho* ratios, small variations in measurement of the *o*-isomer can have a substantial effect on the ratio and that any double chlorination that occurs may also influence the ratio so that the trends are more significant than the absolute ratios. As can be seen from Figure 7, for the most part, the three different types of catalyst produce rather similar results, and there is no evidence to suggest that the more polar groups (OH and OMe) consistently show substantially higher selectivity, as would be expected if the selectivity depended primarily on a strong interaction between the OH region of the substrate and the polar end of the sulphur-containing catalyst. Indeed, for the cases of phenol, *o*-cresol, and *m*-cresol, the greatest selectivity was obtained with a *bis*(methylthio)alkane (**13**) and even with *m*-xylenol a *bis*(methylthio)alkane resulted in

the second-highest selectivity. In most cases, all three kinds of catalysts showed somewhat similar trends as a function of the length of the spacer group. Thus, with *o*-cresol, the highest *para*-selectivities were obtained with the shorter spacer groups (n = 2 or 3), while with *m*-cresol and *m*-xylenol, the highest selectivities were achieved with the longer spacer groups (n = 6 or 9), regardless of the substituent at the ω-position of the catalyst. In these cases, the catalysts with a tetramethylene spacer group (n = 4) also tended to provide somewhat lower selectivity than the general trend with spacer group length might have suggested. The case of phenol itself was rather more difficult to categorise because the effects of chain length were generally not so pronounced, and in this case, there were some significant differences between the different types of the catalyst with the shorter spacer groups, with the dithiaalkanes showing substantially better selectivities than the other catalyst types. Overall, it seemed that the dithiaalkanes offered the best opportunities for highly selective catalysis, and we decided to concentrate future efforts on those.

The results above were difficult to rationalise; thus, we undertook density functional theory (DFT) calculations of the structures of the supposed reactive intermediates in chlorination reactions with the *bis*(methylthio)alkanes of different spacer group lengths [66]. The gas-phase calculations suggested that the intermediate adopts one of two types of structure, depending on the spacer group length. Those with short spacer groups (n = 2–4) adopt a structure involving a strong interaction between the two sulphur atoms, while those with longer spacer groups (n = 6 or 9) adopt a structure where the two sulphur atoms both interact strongly with the chlorine atom (Figure 8). This might offer a possible explanation for why longer spacer groups favour higher *para*-selectivity for phenols with methyl substituents adjacent to the *para*-position (intermediate of structure **14** involved), whereas shorter spacer groups favour *para*-selectivity for phenols without substituents in *meta*-positions (structure **15** involved). More sophisticated calculations, including solvent contributions, would be needed to determine at what spacer group length the changeover occurs, but this may account for the relatively poor selectivity often observed with spacer groups of intermediate length around n = 4 (neither structure particularly favourable).

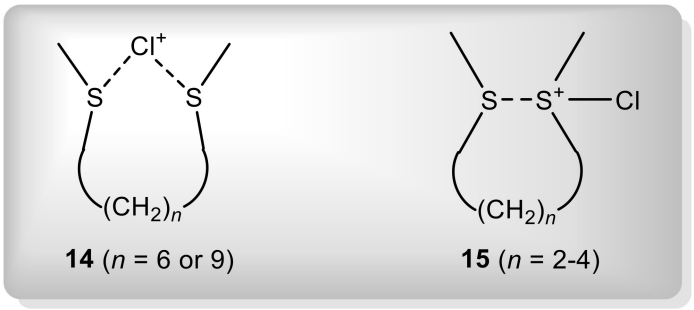
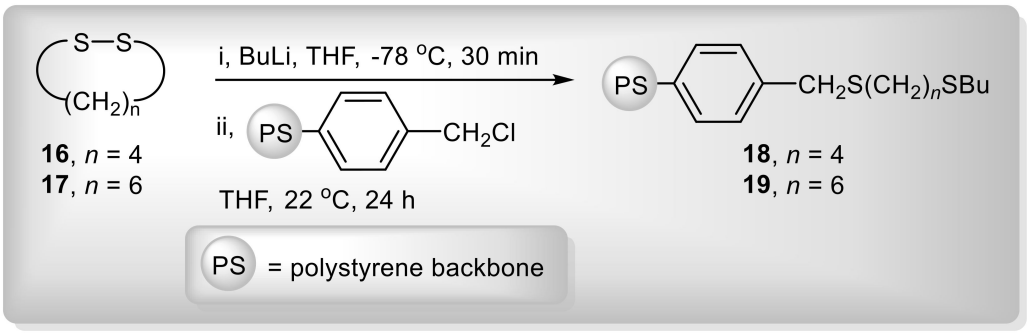


Figure 8. Structures suggested by DFT calculations for active chlorinating agents in presence of dithiaalkanes **13**.

Taking all of the information available, it was clear that the use of appropriate dithiaalkanes as catalysts offered remarkable *para*-selectivity in the chlorination of phenols. For example, 5,18-dithiadocosane (**10**, m = 4, n = 12) resulted in a *para/ortho* ratio of over 20 on chlorination of *m*-cresol, while 2,6-dithiaheptane (**10**, m = 1, n = 3) resulted in a ratio of almost 40 on chlorination of *o*-cresol. However, we still recognised some problems for commercial applications. First, 5,18-dithiadocosane would not be cheap to produce, and at least at the proportion used in these experiments would be needed in quite large quantities (almost 9% by mass of *m*-cresol feedstock), while 2,6-dithiaheptane would have problems with odour similar to the simple dialkyl sulphides. Furthermore, the removal of such catalysts from the product might be difficult. However, the excellent selectivity showed that catalysts with more than one sulphur atom might offer a route to a successful commercial catalyst if they could be easily recovered. We, therefore, considered possible polymeric alternatives that might allow recovery of the catalyst by simple filtration.

4.3. Results with Polymeric Compounds Containing Multiple Sulphur Atoms

The first polymeric sulphides we thought to investigate were derivatives of the Merrifield resin. We developed a method for putting a dithiaalkyl residue onto the resin starting from 1,2-dithiacycloalkanes **16** and **17** (Scheme 2) and tested the two prepared resins **18** and **19** as catalysts for *m*-cresol chlorination [65].



Scheme 2. Method for synthesis of dithiaalkyl-substituted Merrifield resins **18** and **19**.

Use of 0.5 g of the polymers (since polymers are mixtures of many different molecules that may not all behave in the same way, it is more appropriate to relate results to the mass of polymer used rather than to the number of mmol of sulphur or dithiaalkyl units) and 3.8 mmol of aluminium chloride for 100 mmol of *m*-cresol resulted in selectivities that were better than those obtained in the absence of catalyst, and the polymer **19** provided a somewhat better selectivity (*para/ortho* ratio = 17) than that with the comparable 5,12-dithiahexadecane [65]. Furthermore, the material could be readily recovered and used again. However, it would be more difficult to synthesise similar polymers with the very long spacer groups that were particularly selective in the chlorination of *m*-cresol and *m*-xylenol with the dithiaalkane series of catalysts (see Figures 5 and 7), and regardless, such polymers would be very expensive.

Having 1,2-dithiacycloalkanes available, it seemed appropriate to test such compounds, and their polymeric counterparts, as catalysts for chlorination of the target phenols. The specific materials tested (**17** and **20**–**22**) are shown in Figure 9, chosen to represent species with both short and somewhat longer spacer groups, but to be easily synthesised. Chlorination reactions were conducted with each of the four target phenols under conditions similar to those used previously with the other catalysts, and a selection of the results obtained is given in Table 2 [67].

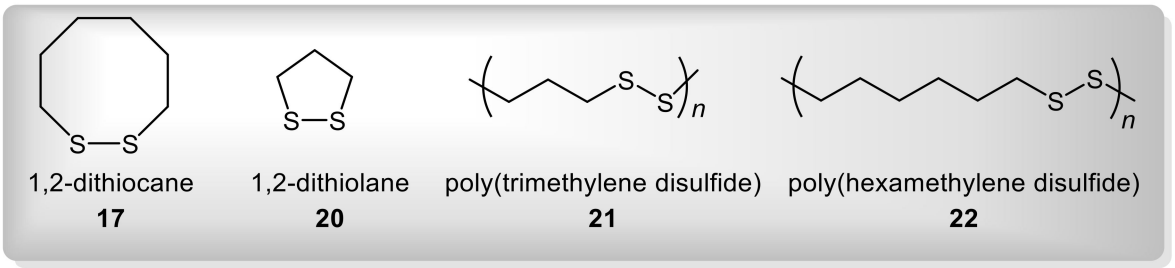


Figure 9. Structures of cyclic and polymeric disulphides **17** and **20**–**22** used in the study.

Table 2. Effect of cyclic and polymeric disulphides **17** and **20**–**22** on the selectivity of chlorination of phenols according to Scheme 1 [a].

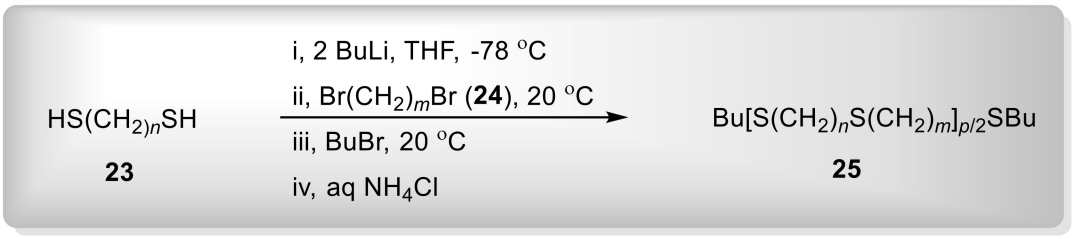
Entry	Catalyst	Spacer Length (*n*)	3:2 Ratio Produced in Presence of the Catalyst			
			Phenol	*o*-Cresol	*m*-Cresol [b]	*m*-Xylenol
1	17	6	12.3	20.6	15.5 (13.0) [c]	11.7
2	20	3	9.6	16.6	13.0 [c]	19.1
3	21	3	8.7	18.7	10.1	23.8
4	22	6	10.2	14.0	10.1	14.9

[a] Conditions: for phenol: 50 mmol substrate, 57.7 mmol SO_2Cl_2, 50 mg $AlCl_3$, 50 mg sulphur compound, 2 h addition of SO_2Cl_2 then 2 h at room temperature. For *o*-cresol: 50 mmol substrate, 57.7 mmol SO_2Cl_2, 250 mg $AlCl_3$, 100 mg sulphur compound, 2 h addition of SO_2Cl_2 then 2 h at room temperature. For *m*-cresol: 50 mmol substrate, 57.7 mmol SO_2Cl_2, 250 mg $AlCl_3$, 100 mg sulphur compound, 2 h addition of SO_2Cl_2 then 2 h at room temperature. For *m*-xylenol: 50 mmol substrate, 57.7 mmol SO_2Cl_2, 25 mg $FeCl_3$, 30 mg sulphur compound, 25 mL DCM, 2 h addition of SO_2Cl_2 then 2 h at room temperature [b] In the case of *m*-cresol, the *ortho*-product **2** is a mixture of 2-chloro-3-methylphenol (minor) and 6-chloro-3-methylphenol (major). [c] Only 50 mg of the catalyst was used in this case.

As can be seen from Table 2, there is no regular pattern to the regioselective effects. For phenol, the longer spacer appears to be better than the smaller spacer and the cyclic compounds appear to be better than the polymers at delivering *para*-selectivity, whereas for *m*-xylenol, exactly the opposite is the case. For *m*-cresol, the spacer length seems to make no difference, but the cyclic compounds appear to be better than the polymers, while for *o*-cresol, the picture is totally confused, with the longer spacer being favoured for the cyclic compounds and the shorter spacer being favoured for the polymers. In only two cases were the selectivities somewhat higher than had been achieved with the previously mentioned catalysts. In addition, 1,2-Dithiocane (**17**) resulted in a *para/ortho* ratio of 12.3 with phenol, but this low molecular weight compound would still suffer the odour problems previously mentioned. Polymer **21** resulted in a *para/ortho* ratio of 23.8 with *m*-xylenol, but in a reducing environment, this polymer could easily give rise to 1,3-propanedithiol, which could again lead to odour issues. Therefore, it was still felt that other polymeric materials needed to be investigated.

4.4. Results with Poly(alkylene sulphide)s

The successful achievement of high *para/ortho* ratios in the chlorination of various phenols with both polymeric disulphides (e.g., *para/ortho* = 23.8 using **21** with *m*-xylenol) and dithiaalkanes (e.g., *para/ortho* = 20.7 using **10**, *m* = 4, *n* = 12 with *m*-cresol) suggested that polymeric equivalents of dithiaalkanes, namely, poly(alkylene sulphide)s, might offer good opportunities for the development of useful selective catalysts. Poly(alkylene sulphide)s have a range of industrial applications [68] but are not generally available for purchase as identifiable specific polymers. We, therefore, decided to synthesise a range of such polymeric materials and initially used a variation of a standard laboratory procedure to do so (Scheme 3). The procedure involved reacting a 1,ω-alkanedithiol **23** with butyllithium to yield the corresponding dilithium dithiolate, then reacting that with a 1,ω-dibromoalkane **24** in the presence of a small quantity of 1-bromobutane (to terminate polymer chains). In principle, the proportion of dibromo and monobromo compounds could be varied to influence the average chain length of the polymers **25** generated, but in practice, we used molar proportions of dithiol:dibromoalkane:1-bromobutane of 100:90:20 in all cases. A selection from the polymers thus generated is recorded in Table 3. The method allowed the synthesis of polymers involving all identical spacer groups by use of dithiols and dibromides of the same chain length, or polymers with spacer groups of alternating length by use of dithiols and dibromides of different chain lengths.

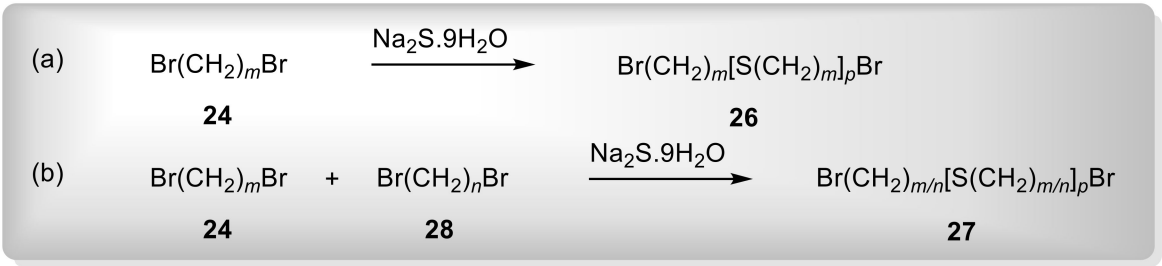


Scheme 3. Controlled synthesis of poly(alkylene sulphide)s.

Table 3. Some polymers **25** prepared according to Scheme 3.

Entry	Polymer Number	*m* of Dibromide 24	*n* of Dithiol 23
1	**25a**	2	2
2	**25b**	3	3
3	**25c**	4	4
4	**25d**	6	6
5	**25e**	8	8
6	**25f**	3	6
7	**25g**	3	9
8	**25h**	3	12
9	**25i**	4	12
10	**25j**	6	12
11	**25k**	8	12

Although this approach provided reliable access to polymers of the desired type, it involved several features that were undesirable from an industrial perspective, including the use of a potentially pyrophoric organolithium reagent, a flammable solvent, and dilute solution. We, therefore, investigated an alternative route involving reaction of 1,ω-dihaloalkanes with sodium sulphide. We were able to develop a viable solvent-free route to poly(alkylene sulphide)s by refluxing cheap sodium sulphide nonahydrate with either dichloroalkanes or dibromoalkanes, but the reactions with dibromoalkanes (Scheme 4) proceeded more quickly and yielded polymers **26** with longer chain lengths [69]. The polymers were simply filtered from the aqueous solution, washed with water, and dried. The use of 1,4-dibromobutane (**24**, $m = 4$) led to only a low yield of polymer **26c** because of preferential formation of tetrahydrothiophene, but the use of other 1,ω-dibromoalkanes led to high yields of polymer. However, longer reflux times (8–24 h instead of 4–5 h) and/or a larger excess of the sodium sulphide (up to 2.5 molar equivalents instead of 1.5) were needed for the polymers with longer spacer groups ($m \geq 8$) in order to provide polymers with significant numbers of repeating units [69]. While this approach could not provide polymers with regularly alternating different spacer groups, by using a mixture of two different dibromoalkanes in the reaction, it was possible to produce polymers **27** with a random sequence of the two different alkylene spacers (Scheme 4). The majority of terminal groups in such polymers **26** and **27** are bromo-substituents. A 1-bromoalkane could be added to reaction mixtures to terminate the polymer chains, enabling control of the average molecular weight and physical properties of the polymers, including allowing the synthesis of liquid polymers [70]. However, in the interests of brevity and potential for recovery of the polymers by filtration, only the results of the use of the simple polymers formed without monobromoalkanes present are reported here. A selection from the range of polymers produced according to Scheme 4 is shown in Table 4. The polymers **25**–**27** possessed no or little odour.



Scheme 4. Syntheses of poly(alkylene sulphide)s **26** and **27**.

Table 4. Some polymers **26** and **27** prepared according to Scheme 4 [a].

Entry	Polymer Number	*m* of Dibromide 24	*n* of Dibromide 28	Average Number of Alkylene Sulphide Units in the Polymer (*p*)
1	**26a**	2	—	Not known [b]
2	**26b**	3	—	24
3	**26c**	4	—	43
4	**26d**	6	—	33
5	**26e**	8	—	20 [c]
6	**27a**	3	6	Not known
7	**27b**	6	8	Not known

[a] Reflux period was 4–6 h unless otherwise stated, and 1.5 equivalents of Na_2S were used. [b] Only 1 h reflux required; the insolubility of the polymer prevented either gel permeation chromatography or nuclear magnetic resonance spectroscopy. [c] Obtained after refluxing for 16 h; after 5 h, the figure was only 3.

In order to test whether the method of preparation of the polymers had any significant influence over their effectiveness, and also to check the effect of spacer group length, the polymers having identical repeating units (**25a**–**e** and **26a**–**e**) were applied in the chlorination of the target phenols (Figure 10) [71,72].

As can be seen, the trends with spacer group length are very similar for the polymers made by the two different methods, but generally, those made by the sodium sulphide route resulted in somewhat lower *para*/*ortho* ratios than those made by the lithiated dithiol route. This could imply an effect of the different terminal groups, or of the presence of disulphide units in polymers **26**, or of different average numbers of repeating units in the polymers made by the different methods, but it is also possibly a function of the presence of small molecule impurities in the polymers made by the sodium sulphide method because these polymers were washed only with water and had never been touched by any organic solvent, whereas the polymers prepared by the lithiated dithiol route were prepared in an organic solvent and were further washed by an organic solvent. Tests with polymers made by the use of dichloroalkanes in the sodium sulphide route showed no particular advantage over those produced from dibromoalkanes and were not studied further [73]. The trends with spacer group length (Figure 10) matched those observed previously with dithiaalkanes, with the shorter spacers, particularly m = 3 or 4, being more selective for chlorination of phenol and *o*-cresol, while the longer spacers, m = 6 or 8, were more selective for *m*-cresol and *m*-xylenol. It was also of interest to see whether there were any significant effects from having polymers with spacers of different lengths. Therefore, a similar series of tests were carried out with such polymers (Figure 11) [71,72].

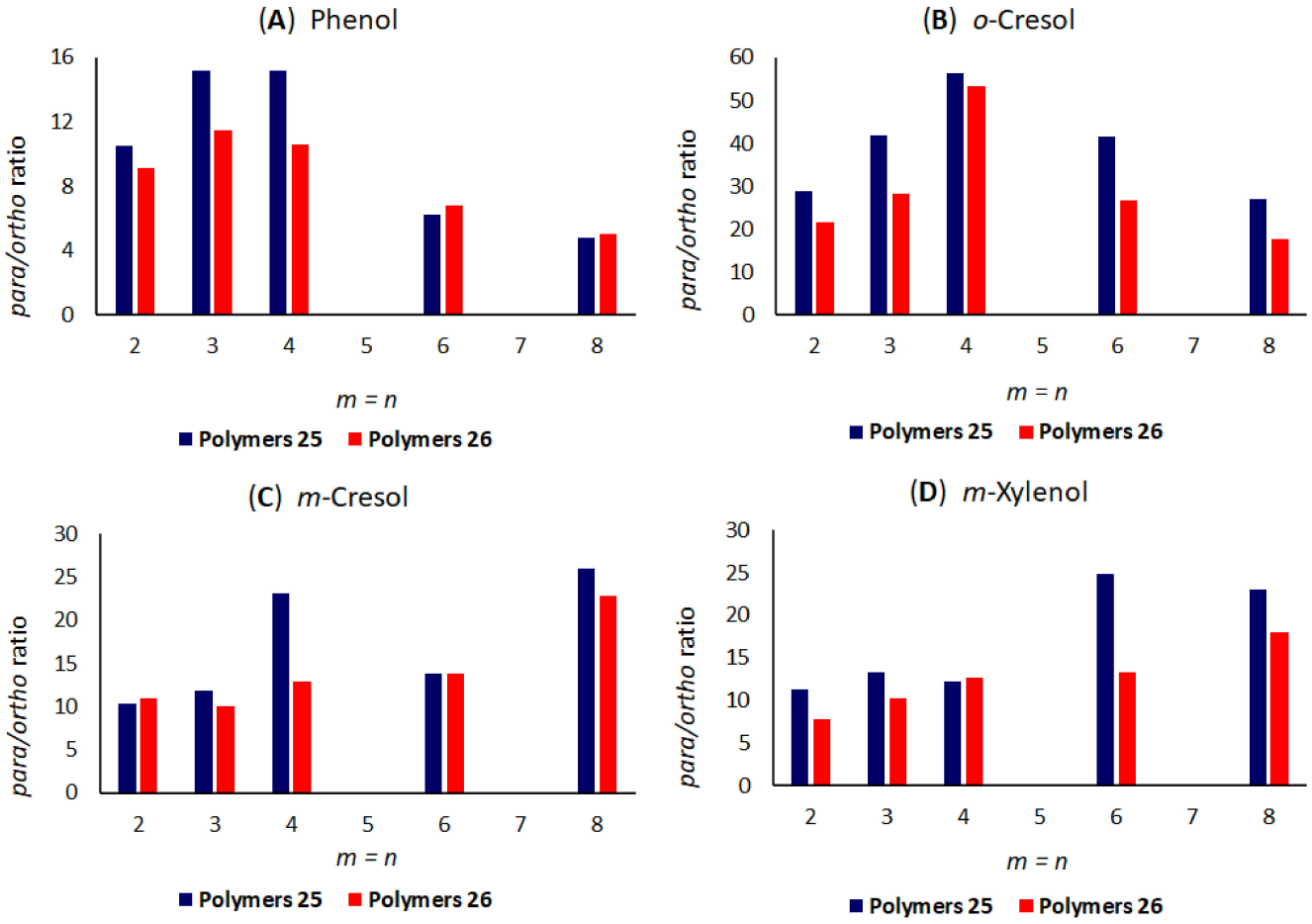


Figure 10. Effect of polymers **25** and **26** on the selectivity of chlorination of phenols according to Scheme 1. Conditions: For phenol (Chart **A**): 100 mmol substrate, 110 mmol SO_2Cl_2, 100 mg $AlCl_3$, 100 mg sulphur compound, 2 h addition of SO_2Cl_2 then 2 h at room temperature. For *o*-cresol (Chart **B**) and *m*-cresol (Chart **C**): 100 mmol substrate, 110 mmol SO_2Cl_2, 500 mg $AlCl_3$, 200 mg sulphur compound, 2 h addition of SO_2Cl_2 then 2 h at room temperature. For *m*-xylenol (Chart **D**): 100 mmol substrate, 110 mmol SO_2Cl_2, 100 mg $FeCl_3$, 200 mg sulphur compound, 25 mL DCM, 2 h addition of SO_2Cl_2 then 2 h at room temperature. [b] In the case of *m*-cresol, the *ortho*-product **2** is a mixture of 2-chloro-3-methylphenol (minor) and 6-chloro-3-methylphenol (major).

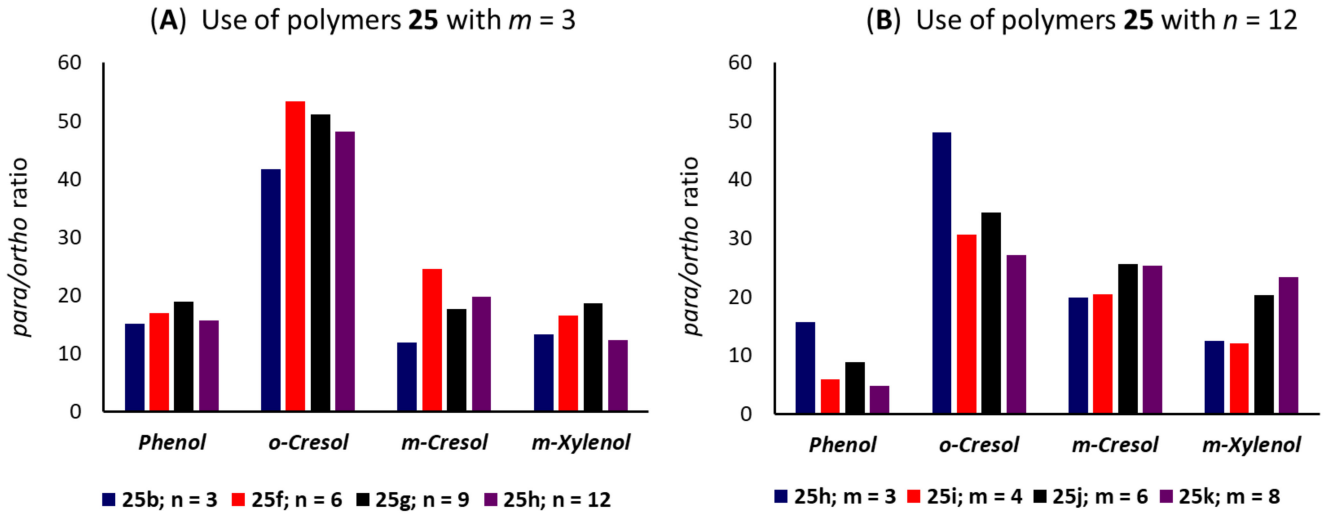


Figure 11. Effect of polymers **25** having $m \neq n$ on the selectivity of chlorination of phenols according to Scheme 1. Conditions were as described in the footnote to Figure 10. (**A**) Use of polymers **25** with m = 3 and n as indicated at the foot of the chart; (**B**) Use of polymers **25** with n = 12 and m as indicated at the foot of the chart.

From Chart A in Figure 11, it appears that for phenol and *o*-cresol there might be a small advantage from having the second spacer group longer if the first is a trimethylene spacer, and also, less surprisingly, an advantage from having a longer second spacer for *m*-cresol and *m*-xylenol. From Chart B, with the second spacer fixed at $n = 12$, it is clear that for phenol and *o*-cresol, it is advantageous to have a shorter first spacer, particularly $m = 3$, while for *m*-cresol and *m*-xylenol, it is disadvantageous to have a short first spacer. These findings are consistent with the previous conclusions that shorter spacers are generally somewhat better for *para*-selectivity for the phenols with no substituents at positions adjacent to the desirable substitution site, whereas longer spacers are generally better for those with substituents in that position. We also tested the mixed spacer polymers **27** made by the sodium sulphide method, but they performed as would be expected from the results with the single spacer polymers **26**, and no further discussion is warranted.

The results reported in Figures 10 and 11 were conducted with 100 mg of poly(alkylene sulphide) catalyst in the cases of phenol and *m*-xylenol and with 200 mg of polymer in the cases of *o*- and *m*-cresols, for reactions involving 100 mmol of the substrate. In order to gauge the importance of the amount of catalyst on the selectivity, several catalysts were tested at three different levels (200 mg, 100 mg, and 50 mg) with the *o*- and *m*-cresols. As expected, most of the catalysts tried led to a reduction in selectivity as the quantity of catalyst was reduced. However, in the case of polymer **26b** for *o*-cresol and **27a** for *m*-cresol, there was virtually no difference in the level of selectivity with the three different amounts of catalyst (Figure 12) [72]. The reason for these unexpected results was not clear, but it prompted a much wider study of the effects of the amount of sulphuryl chloride used, the quantity of catalyst, the quantity of Lewis acid, the reaction temperature and time, and in the case of *m*-xylenol the nature and quantity of the solvent used [70–72]. The result of such studies was the identification of some procedures that provided exceptional selectivities with quite tiny amounts of catalyst. A few examples are given in Table 5.

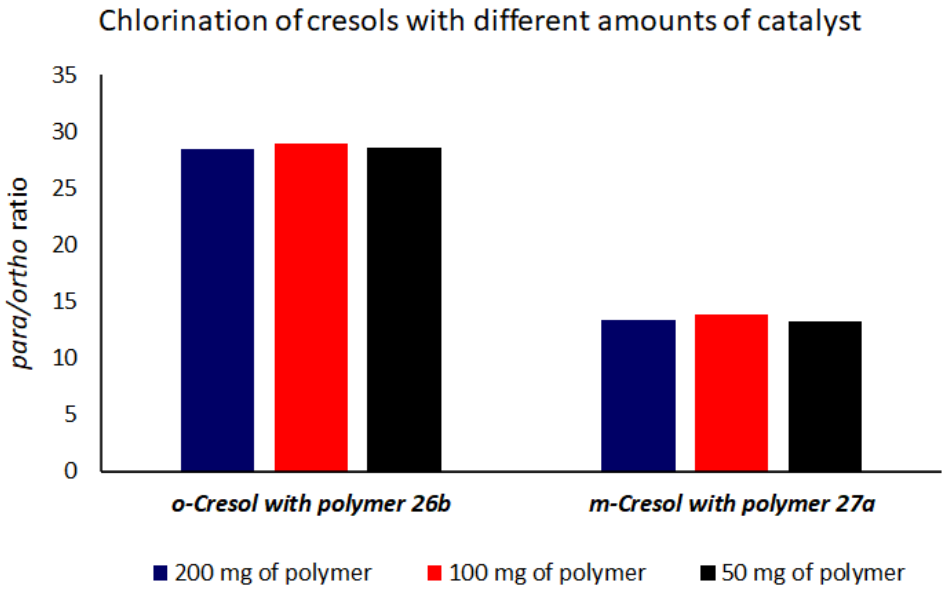


Figure 12. Chlorination of cresols with different amounts of certain catalysts. Conditions: For *o*-cresol: 100 mmol *o*-cresol; 105 mmol SO_2Cl_2; 500 mg $AlCl_3$; 20 °C, 4 h; for *m*-cresol: 100 mmol *o*-cresol; 106 mmol SO_2Cl_2; 200 mg $AlCl_3$ (100 mg for the case of 50 mg catalyst); room temperature, 4 h.

Table 5. Some results with small quantities of catalysts [a].

Entry	Substrate	Catalyst (mg)	Lewis Acid (mg)	SO_2Cl_2 (mmol)	Components of Product Mixture (Absolute %)			
					2-Cl	4-Cl	Others [c]	*para*/*ortho* Ratio
1	*o*-Cresol	**26b** (3)	$AlCl_3$ (20)	105	4.5	95.1	0.1	21.4
2	*m*-Cresol	**27a** (3)	$AlCl_3$ (50)	105	7.7	91.6	0.3	11.9
3	*m*-Xylenol [b]	**26d** (3)	$FeCl_3$ (20)	105	5.6	93.5	0.8	16.7
4	*m*-Xylenol [b]	**26d** (5)	$FeCl_3$ (50)	105	2.8	94.9	2.2	33.9
5	Phenol	**27a** (20)	$AlCl_3$ (50)	110	7.5	90.8	1.5	12.0
6	Phenol (di)	**26a** (20)	$AlCl_3$ (30)	210	0.8	91.8	7.0	109.3
7	Phenol (di)	**26a** (50)	$AlCl_3$ (100)	210	0.7	94.0	5.0	134.3

[a] Conditions: 100 mmol of the substrate; unless otherwise stated, reactions were run at 20 °C or at room temperature. [b] Reactions were conducted in 17.5 mL of tetrachloroethylene ("perc") and at 40–50 °C. [c] The other identified species were unreacted substrate, doubly chlorinated substrate, or (in the case of planned double chlorination of phenol) monochlorinated substrate, namely, 2-chlorophenol and 4-chlorophenol.

The results in Table 5 do not necessarily represent either the highest yields of the desired product or the highest *para*-selectivities that could be achieved. Greater yields and selectivities were attained by the use of one or more of the following approaches: use of a catalyst of type **25** rather than one of type **26** or **27**; use of a larger quantity of catalyst and/or of Lewis acid; use of a different Lewis acid (particularly replacing ferric chloride by aluminium chloride); variation of the reaction concentration (in the case of *m*-xylenol) or of other reaction conditions. However, such modifications would typically provide improvements of only 1–3% in the absolute yield of the desired product, while also introducing extra costs or challenges for commercial applicability. Therefore, the examples shown were thought to represent good opportunities for further development. In the case of *m*-xylenol, when the reaction mixtures were cooled, the desired product crystallised out of the tetrachloroethylene solution. Filtration and washing with a small amount of tetrachloroethylene typically left a solid in around 90% yield that was around 99.7–99.9% pure without further crystallisation. The remaining product could be recovered as a solid that was typically around 97–98% pure by the concentration of the mother liquors and washings.

The use of just 3 mg of catalyst **26b**, **26d**, or **27a** for 100 mmol of substrate corresponds to the use of 3 kg for chlorination of 10.8 tons of cresol or 12.2 tons of xylenol, and if this were to result in 90% isolated yield of pure *para*-chloro product, it would provide 12.8 tons of 4-chlorocresol or 14.1 tons of 4-chloroxylenol. These are quantities that could be accommodated in a typical industrial batch reactor. Using standard laboratory glassware, it was easily possible to synthesise over 200 g of catalyst **26b**, 250 g of **27a**, or 300 g of **26d** in a single batch, and by preparing numerous batches, we were able to produce 6 kg of **26d** so that it could be tested at commercial scale for chlorination of *m*-xylenol [70]. After successful testing, a commercial process was put into operation for the production of 4-chloro-3,5-dimethylphenol (*para*-chloro-*meta*-xylenol, PCMX). Thus, the ultimate goal of the research project has been demonstrated. As a bonus, the poly(alkylene sulphide)s prepared offer opportunities for other applications, and we have shown, for example, that the poly(propylene sulphide) is a useful carrier of borane (BH_3)to create a reagent that acts in a way similar to the widely used dimethyl sulphide-borane complex, but without the volatility, odour or hazards associated with dimethyl sulphide [74,75].

5. Conclusions

para-Regioselective chlorination of various phenols using sulphuryl chloride in the presence of various sulphur-containing catalysts has been successfully developed. The catalysts used included dithiaalkanes, methylthioalkanes, tetrahydrothiopyrans, dialkyl sulphides, cyclic disulphides, polymeric disulphides, sulphur-containing Merrifield resins, and poly(alkylene sulphide)s, along with a Lewis acid (aluminium or ferric chloride) as an activator. In most cases, the chlorination processes involved the use of just a small excess over the stoichiometric quantity of sulphuryl chloride in the absence of any solvent under

mild conditions. Notably, poly(alkylene sulphide)s containing longer spacer groups are particularly *para*-selective in the chlorination of *m*-cresol and *m*-xylenol, while ones with shorter spacers are particularly *para*-selective in the chlorination of phenol, 2-chlorophenol, and *o*-cresol. The developed processes provided some of the highest *para*/*ortho* ratios ever reported for the chlorination of phenols, and the process for the production of 4-chloro-3,5-dimethylphenol has been used commercially.

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References

1. Palleros, D.R. *Experimental Organic Chemistry*; John Wiley Sons: New York, NY, USA, 2000.
2. Chikhradze, N.; Nadirashvili, M.; Khomeriki, S.; Varshanidze, I. The synthesis of phenyl acetylene phenols for development of new explosives. *IOP Conf. Ser. Earth Environ. Sci.* **2017**, *95*, 042030. [CrossRef]
3. Khabarov, Y.G.; Patrakeev, A.A.; Veshnyakov, V.A.; Kosyakov, D.S.; Ul'yanovskii, N.V.; Garkotin, A.Y. One-step synthesis of picric acid from phenol. *Org. Prep. Proced. Int.* **2017**, *49*, 178–181. [CrossRef]
4. Benkhaya, S.; M'rabet, S.; El Harfia, A. Classifications, properties, recent synthesis and applications of azo dyes. *Heliyon* **2020**, *6*, e03271. [CrossRef]
5. Foti, M.C. Antioxidant properties of phenols. *J. Pharm. Pharmacol.* **2007**, *59*, 1673–1685. [CrossRef]
6. Hesse, W. Phenolic Resins. In *Ullmann's Encyclopedia of Industrial Chemistry*; Wiley-VCH: Weinheim, Germany, 2002. [CrossRef]
7. Cook, A.M. Phenolic disinfectants. *J. Pharm. Pharmacol.* **1960**, *12*, 19T–28T. [CrossRef]
8. Reddy, V.P.; Prakash, G.K.S. Electrophilic Reactions of Phenols. In *PATAI's Chemistry of Functional Groups*; John Wiley Sons: New York, NY, USA, 2009. [CrossRef]
9. Wiley-VCH. *Ullmann's Encyclopedia of Industrial Chemistry*, 6th ed.; Wiley-VCH: Weinheim, Germany, 1998.
10. Fagan, K.; John, K.P. The effect of the phenoxyacetic acid herbicides 2,4,5-trichlorophenoxyacetic acid and 2,4-dichlorophenoxyacetic acid as ascertained by direct experimentation. *Residue Rev.* **1984**, *92*, 29–58. [CrossRef]
11. Favaro, G.; De Leo, D.; Pastore, P.; Magno, F.; Ballardin, A. Quantitative determination of chlorophenols in leather by pressurized liquid extraction and liquid chromatography with diode-array detection. *J. Chromatogr. A* **2008**, *1177*, 36–42. [CrossRef] [PubMed]
12. Igbinosa, E.O.; Odjadjare, E.E.; Chigor, V.N.; Igbinosa, I.H.; Emoghene, A.O.; Ekhaise, F.O.; Igiehon, N.O.; Idemudia, O.G. Toxicological profile of chlorophenols and their derivatives in the environment: The public health perspective. *Chemosphere* **2011**, *83*, 1297–1306. [CrossRef]
13. World Health Organization. *WHO Model Formulary 2008*; Stuart, M.C., Kouimtzi, M., Hill, S.R., Eds.; World Health Organization: Geneva, Switzerland, 2009.
14. Griffiths, C.; Barker, J.; Bleiker, T.O.; Chalmers, R.; Creamer, D. *Rook's Textbook of Dermatology*, 9th ed.; John Wiley Sons: Oxford, UK, 2017.
15. Digison, M.B. A review of anti-septic agents for pre-operative skin preparation. *Plast. Surg. Nurs.* **2007**, *27*, 185–189. [CrossRef] [PubMed]
16. El-Hiti, G.A.; Smith, K.; Hegazy, A.S. Catalytic, green and regioselective Friedel-Crafts acylation of simple aromatics and heterocycles over zeolites. *Curr. Org. Chem.* **2015**, *19*, 585–598. [CrossRef]
17. Smith, K.; El-Hiti, G.A. Use of zeolites for green and *para*-selective electrophilic aromatic substitution reactions. *Green Chem.* **2011**, *13*, 1579–1608. [CrossRef]
18. Smith, K.; El-Hiti, G.A. Regioselective electrophilic aromatic substitution reactions over reusable zeolites. *Curr. Org. Chem.* **2006**, *10*, 1603–1625. [CrossRef]
19. Smith, K.; El-Hiti, G.A. Regioselective control of electrophilic aromatic substitution reactions. *Curr. Org. Synth.* **2004**, *1*, 253–274. [CrossRef]
20. Smith, K.; Al-Khalaf, A.K.H.; El-Hiti, G.A.; Pattisson, S. Highly regioselective di-*tert*-amylation of naphthalene over reusable HM zeolite catalyst. *Green Chem.* **2012**, *14*, 1103–1110. [CrossRef]

21. Smith, K.; Roberts, S.D.; El-Hiti, G.A. Study of regioselective dialkylation of naphthalene in the presence of reusable zeolite catalysts. *Org. Biomol. Chem.* **2003**, *1*, 1552–1559. [CrossRef] [PubMed]
22. Smith, K.; El-Hiti, G.A.; Jayne, A.J.; Butters, M. Acetylation of aromatic ethers using acetic anhydride over solid acid catalysts in a solvent-free system. Scope of the reaction for substituted ethers. *Org. Biomol. Chem.* **2003**, *1*, 1560–1564. [CrossRef] [PubMed]
23. Smith, K.; El-Hiti, G.A.; Jayne, A.J.; Butters, M. Acylation of aromatic ethers over solid acid catalysts: Scope of the reaction with more complex acylating agents. *Org. Biomol. Chem.* **2003**, *1*, 2321–2325. [CrossRef]
24. Smith, K.; Ewart, G.M.; El-Hiti, G.A.; Randles, K.R. Study of regioselective methanesulfonylation of simple aromatics with methanesulfonic anhydride in the presence of reusable zeolite catalysts. *Org. Biomol. Chem.* **2004**, *2*, 3150–3154. [CrossRef]
25. Smith, K.; Alotaibi, M.H.; El-Hiti, G.A. Regioselective nitration of 2- and 4-nitrotoluenes over systems comprising nitric acid, an acid anhydride and a zeolite. *Arkivoc* **2014**, *2014*, 301–309. [CrossRef]
26. Smith, K.; Alotaibi, M.H.; El-Hiti, G.A. Regioselective dinitration of simple aromatics over zeolite Hβ/nitric acid/acid anhydride systems. *Arkivoc* **2014**, *2014*, 107–123. [CrossRef]
27. Smith, K.; Alotaibi, M.H.; El-Hiti, G.A. Highly regioselective dinitration of toluene over zeolite Hβ. *J. Catal.* **2013**, *297*, 244–247. [CrossRef]
28. Smith, K.; Ajarim, M.D.; El-Hiti, G.A. Regioselective nitration of deactivated aromatics using acyl nitrates over reusable acidic zeolite catalysts. *Catal. Lett.* **2010**, *134*, 270–278. [CrossRef]
29. Smith, K.; Liu, S.; El-Hiti, G.A. Regioselective mononitration of simple aromatic compounds under mild conditions in ionic liquid. *Ind. Eng. Chem. Res.* **2005**, *44*, 8611–8615. [CrossRef]
30. Smith, K.; Musson, A.; DeBoos, G.A. A novel method for the nitration of simple aromatic compounds. *J. Org. Chem.* **1998**, *63*, 8448–8454. [CrossRef]
31. Smith, K.; Musson, A.; DeBoos, G.A. Superior methodology for the nitration of simple aromatic compounds. *Chem. Commun.* **1996**, 469–470. [CrossRef]
32. Smith, K.; Butters, M.; Paget, W.E.; Nay, B. New reagent systems for electrophilic chlorination of aromatic compounds: Organic chlorine-containing compounds in the presence of silica. *Synthesis* **1985**, 1155–1156. [CrossRef]
33. Mistry, A.G.; Smith, K.; Bye, M.R. A superior synthetic method for the bromination of indoles and benzimidazoles. *Tetrahedron Lett.* **1986**, *27*, 1051–1054. [CrossRef]
34. Smith, K.; James, D.M.; Mistry, A.G.; Bye, M.R.; Faulkner, D.J. A new method for bromination and polybromination of carbazoles, β-carbolines and iminodibenzyls by using *N*-bromosuccinimide and silica gel. *Tetrahedron* **1992**, *48*, 7479–7488. [CrossRef]
35. Jigajinni, V.B.; Paget, W.E.; Smith, K. The synthesis of alkyl chlorides *via* reaction of trialkylboranes with dichloramine-T or *N,N*-dichlorourethane. *J. Chem. Res.* **1981**, 376–377.
36. Mistry, A.G.; Smith, K.; Bye, M.R. Solid Supported Halogenations: A Novel Method for Bromination of Heterocycles. In *Bromine Compounds: Chemistry and Applications*; Price, D., Iddon, B., Wakefield, B.J., Eds.; Elsevier: Amsterdam, The Netherlands, 1988; pp. 277–295.
37. Smith, K. Controlled Bromination with the Help of Microporous Solids. In *Advances in Organobromine Chemistry I*; Desmurs, J.-R., Gérard, B., Eds.; Elsevier: Amsterdam, The Netherlands, 1991; pp. 5–21.
38. Smith, K.; Butters, M.; Paget, W.E.; Goubet, D.; Fromentin, E.; Nay, B. Highly selective monochlorination of aromatic compounds under mild conditions by *tert*-butyl hypochlorite in the presence of zeolites. *Green Chem.* **1999**, *1*, 83–90. [CrossRef]
39. Smith, K.; He, P.; Taylor, A. Highly selective liquid phase *para*-bromination of phenyl acetate catalysed by zeolites and metal acetates. *Green Chem.* **1999**, *1*, 35–38. [CrossRef]
40. Smith, K.; El-Hiti, G.A.; Hammond, M.E.W.; Bahzad, D.; Li, Z.; Siquet, C. Highly efficient and selective electrophilic and free radical catalytic bromination reactions of simple aromatic compounds in the presence of reusable zeolites. *J. Chem. Soc. Perkin Trans. 1* **2000**, 2745–2752. [CrossRef]
41. Smith, K.; Bahzad, D. Highly efficient *para*-Selective bromination of simple aromatic substrates by means of bromine and a reusable zeolite. *Chem. Commun.* **1996**, 467–468. [CrossRef]
42. Maloney, V.; Szczepansk, Z.; Smith, K. Introduction of a simple experiment for the undergraduate organic chemistry laboratory demonstrating the Lewis acid and shape selective properties of zeolites. *J. Chem. Ed.* **2017**, *94*, 1343–1346. [CrossRef]
43. Smith, K.; Butters, M.; Nay, B. High *ortho*-selectivity in the chlorination of phenols with *N*-chlorodialkylamines in the presence of silica. *Tetrahedron Lett.* **1988**, *29*, 1319–1322. [CrossRef]
44. Smith, K.; Ajarim, M.D.; El-Hiti, G.A.; Peters, C. Catalytic mononitration of phenol using *iso*-propyl nitrate over zeolite catalysts. *Topics Catal.* **2009**, *52*, 1696–1700. [CrossRef]
45. Gnaim, J.M.; Sheldon, R.A. Shape-selective *para*-chlorination of phenol using sulfuryl chloride with the aid of microporous catalysts. *Tetrahedron Lett.* **2004**, *45*, 9397–9399. [CrossRef]
46. Smith, K.; James, D.M.; Matthews, I.; Bye, M.R. Selective *para*-bromination of phenols *via* a regenerable polymer-bound tetraalkylammonium tribromide. *J. Chem. Soc. Perkin Trans. 1* **1992**, 1877–1878. [CrossRef]
47. Sullivan, J.D. *Para*-Halogenation of phenols. *Chem. Abstr.* **1957**, *51*, 77109.
48. Nishihara, A.; Kato, H. Chlorination of phenols. *Chem. Abstr.* **1974**, *81*, 120196.
49. March, J. *Advanced Organic Chemistry: Reactions, Mechanisms and Structure*, 4th ed.; Wiley: New York, NY, USA, 1992.
50. Xin, H.; Yang, S.; An, B.; An, Z. Selective water-based oxychlorination of phenol with hydrogen peroxide catalysed by manganous sulfate. *RSC Adv.* **2017**, *7*, 13467–13472. [CrossRef]

51. Nahide, P.D.; Ramadoss, V.; Juárez-Ornelas, K.A.; Satkar, Y.; Ortiz-Alvarado, R.; Cervera-Villanueva, J.M.; Alonso-Castro, Á.J.; Zapata-Morales, J.R.; Ramírez-Morales, M.A.; Ruiz-Padilla, A.J.; et al. In situ formed I^{III}-based reagent for the electrophilic ortho-chlorination of phenols and phenol ethers: The use of PIFA-$AlCl_3$ System. *Eur. J. Org. Chem.* **2018**, *2018*, 485–493. [CrossRef]
52. Xiong, X.D.; Yeung, Y.-Y. Ammonium salt-catalyzed highly practical *ortho*-selective monohalogenation and phenylselenation of phenols: Scope and applications. *ACS Catal.* **2018**, *8*, 4033–4043. [CrossRef]
53. Bugnet, E.A.; Brough, A.R.; Greatrex, R.; Kee, T.P. On the *para*-selective chlorination of *ortho*-cresol. *Tetrahedron* **2002**, *58*, 8059–8065. [CrossRef]
54. Watson, W.D. Chlorination with sulfuryl chloride. *Chem. Abstr.* **1976**, *84*, 43612.
55. Watson, W.D. The regioselective *para* chlorination of 2-methylphenol. *Tetrahedron Lett.* **1976**, *17*, 2591–2594. [CrossRef]
56. Watson, W.D. Regioselective *para*-chlorination of activated aromatic compounds. *J. Org. Chem.* **1985**, *50*, 2145–2148. [CrossRef]
57. Binns, J.S.; Braithwaite, M.J. *p*-Chlorophenol. *Chem. Abstr.* **1978**, *88*, 120784.
58. Ogata, Y.; Kimura, M.; Kondo, Y.; Katoh, H.; Chen, F.-C. Orientation in the chlorination of phenol and of anisole with sodium and *t*-butyl hypochlorites in various solvents. *J. Chem. Soc. Perkin. Trans. 2* **1984**, 451–453. [CrossRef]
59. Olah, G.A.; Ohannesian, L.; Arvanaghi, M. Synthetic methods and reactions; 127. Regioselective *para* halogenation of phenols, phenol ethers and anilines with halodimethylsulfonium halides. *Synthesis* **1986**, 868–870. [CrossRef]
60. Tzimas, M.; Smith, K.; Brown, C.M.; Payne, K. Chlorination of aromatic compounds and catalysts therefor. *Chem. Abstr.* **1998**, *129*, 260219.
61. Smith, K.; Tzimas, M.; Brown, C.M.; Payne, K. Dialkyl sulfides as selective catalysts for the chlorination of phenols. *Sulfur Lett.* **1999**, *22*, 89–101.
62. Tzimas, M. Selective Control of Chlorination of Phenols. Ph.D. Thesis, University of Wales Swansea, Swansea, UK, 1995.
63. Smith, K.; Williams, D.; El-Hiti, G.A. Regioselective chlorination of phenols in the presence of tetrahydrothiopyran derivatives. *J. Sulfur Chem.* **2019**, *40*, 529–538. [CrossRef]
64. Tzimas, M.; Smith, K.; Brown, C.M.; Payne, K. Chlorination of aromatic compounds and catalysts therefor. *Chem. Abstr.* **1998**, *129*, 275696.
65. Smith, K.; Tzimas, M.; Brown, C.M.; Payne, K. Dithiaalkanes and modified Merrifield resins as selective catalysts for the chlorination of phenols. *Sulfur Lett.* **1999**, *22*, 103–123.
66. Smith, K.; Al-Zuhairi, A.J.; Elliot, M.C.; El-Hiti, G.A. Regioselective synthesis of important chlorophenols in the presence of methylthioalkanes with remote SMe, OMe or OH substituents. *J. Sulfur Chem.* **2018**, *39*, 607–621. [CrossRef]
67. Smith, K.; Al-Zuhairi, A.J.; El-Hiti, G.A.; Alshammari, M.B. Comparison of cyclic and polymeric disulfides as catalysts for the regioselective chlorination of phenols. *J. Sulfur Chem.* **2015**, *36*, 74–85. [CrossRef]
68. Vo, C.D.; Kilcher, G.; Tirelli, N. Polymers and sulfur: What are organic polysulfides good for? Preparative strategies and biological applications. *Macromol. Rapid Commun.* **2009**, *30*, 299–315. [CrossRef]
69. Smith, K.; El-Hiti, G.A.; Al-Zuhairi, A.J. The synthesis of polymeric sulfides by reaction of dihaloalkanes with sodium sulfide. *J. Sulfur Chem.* **2011**, *32*, 521–531. [CrossRef]
70. Smith, K.; Hegazy, A.S.; El-Hiti, G.A. Previously unpublished results from the authors' group. 2020.
71. Smith, K.; Hegazy, A.S.; El-Hiti, G.A. The use of polymeric sulfides as catalysts for the *para*-regioselective chlorination of phenol and 2-chlorophenol. *J. Sulfur Chem.* **2020**, *41*, 1–12. [CrossRef]
72. Smith, K.; Hegazy, A.S.; El-Hiti, G.A. *para*-Selective chlorination of cresols and *m*-xylenol using sulfuryl chloride in the presence of poly(alkylene sulfide)s. *J. Sulfur Chem.* **2020**, *41*, 345–356. [CrossRef]
73. Smith, K.; Al-Zuhairi, A.J.; El-Hiti, G.A. Previously unpublished results from the authors' group. 2012.
74. Smith, K.; Balakit, A.A.; Pardasani, R.T.; El-Hiti, G.A. New polymeric sulfide-borane complexes: Convenient hydroborating and reducing reagents. *J. Sulfur Chem.* **2011**, *32*, 287–295. [CrossRef]
75. Smith, K.; Balakit, A.A.; El-Hiti, G.A. Poly(propylene sulfide)–borane: Reagent for organic synthesis. *Tetrahedron* **2012**, *68*, 7834–7839. [CrossRef]