

# Electrophilic Chlorination of 4-Methylphenols with Molecular Chlorine. Synthesis of Dimethoxy Aromatics by Methanolysis of 4-Chloro-4-methylcyclohexa-2,5-dienones

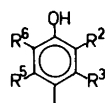
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The chlorination of *p*-cresol (*1a*), 2,4-dimethylphenol (*1b*), 3,4-dimethylphenol (*1c*), 2,4,5-trimethylphenol (*1d*), 2,4,6-trimethylphenol (*1e*) and the various possible mono- and dichloro derivatives of these phenols (*3a–d*, *6a* and *6c*) with molecular chlorine was investigated in dichloromethane or dimethyl formamide solution. The 2,6-substituted *p*-cresol derivatives all give quantitative yields of 4-chloro-4-methylcyclohexa-2,5-dienones (*5b*, *5d*, *7a*, *7c* and *2e*), whereas the less substituted *p*-cresol derivatives give a 20–50% yield of the corresponding 4-chloro-4-methylcyclohexa-2,5-dienones (*2a–d*, *5a* and *5c*), the other products being chlorinated phenols. Treatment of 4-chloro-4-methylcyclohexa-2,5-dienones with at least one of the double bonds of the ring unsubstituted (*2a–c* and *4a*) with methanol gave a quantitative yield of a 1,3-dimethoxybenzene derivative (*9a–c* and *10*), whereas similar treatment of 4-chloro-2,4,5-trimethylcyclohexa-2,5-dienone (*2d*) gave 5-methoxy-2,3-dimethylbenzyl methyl ether (*11*). Treatment of the other 4-chlorodienones with methanol gave the corresponding 4-methoxydienones. Electrophilic chlorination of certain *p*-cresol derivatives followed by methanolysis hence is a facile although low-yield method for 3-methoxylation or selective side chain oxidation of these *p*-cresol derivatives.

In a previous publication,<sup>1</sup> we described a novel high yield synthesis of 4-chloro-4-methylcyclohexa-2,5-dienone (*2a*) from *p*-cresol (*1a*) by chlorination with antimony pentachloride in dichloromethane (DCM) at low temperature. In the same publication a number of reactions with *2a* were described which demonstrated that *2a* is a useful synthon.

However, the work-up of the reaction mixture from chlorination with antimony pentachloride was cumbersome, and therefore a search for alternative chlorination reagents was initiated. Attempts were made to oxidize 4-alkylphenols electrochemically in the presence of chloride ions, in the hope that anodically generated phenoxonium ion would react with chloride ion to give the desired chlorodienone. From previous studies<sup>2</sup> we know that 4-alkylphenoxonium ions reacts with nucleophiles preferentially in the 4-position. Actually, anodic oxidation of *p*-cresol in dimethyl formamide (DMF) containing hydrogen chloride gave a modest yield (20%) of *2a*. However, electroanalytic studies re-



1a–e

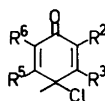
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b:  $R^2=Me, R^3=R^5=R^6=H$

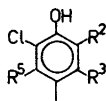
c:  $R^2=R^5=R^6=H, R^3=Me$

d:  $R^2=R^5=Me, R^3=R^6=H$

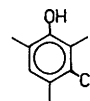
e:  $R^2=R^6=Me, R^3=R^5=H$



2a–e



3a–d



4

vealed that no oxidation of *p*-cresol occurred in this system. Only chlorid ion was oxidized to molecular chlorine, which in turn reacted with *p*-cresol to give a mixture of 2a and 2-chloro-*p*-cresol (3a). We therefore started a detailed study of the chlorination of *p*-cresol and other 4-alkylphenols (1b–e) by molecular chlorine to see if it was possible to use this method for the preparation of 4-alkyl-4-chlorocyclohexa-2,4-dienones. In the course of this study a similar investigation of the *ipso* chlorination of

4-alkylphenols in acetic anhydride has been published.<sup>3</sup>

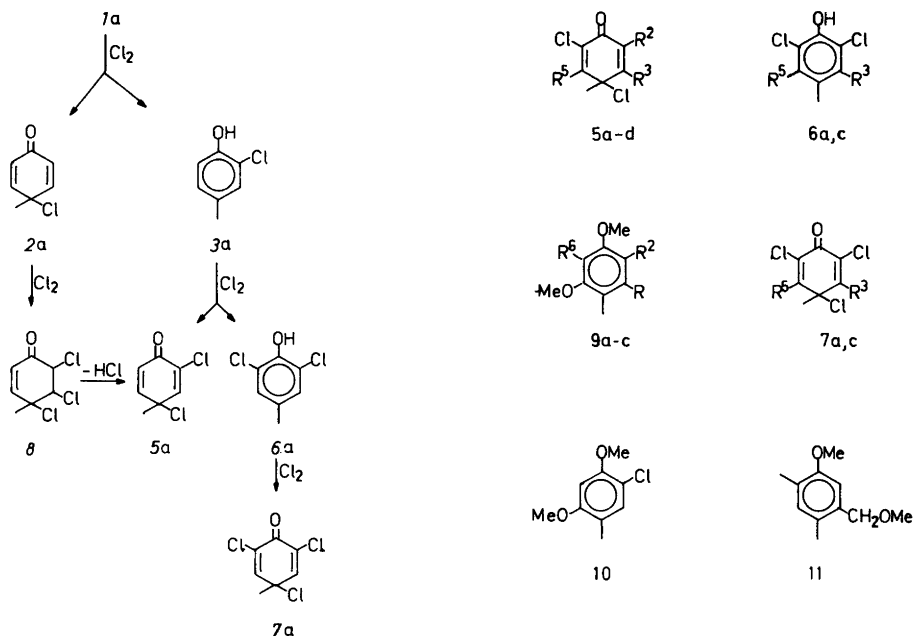
## RESULTS AND DISCUSSION

The effect of the amount of chlorine, solvent, temperature, and added Friedel-Crafts catalyst on the product distribution in the chlorination of *p*-cresol was studied in detail, and the results are given in Table 1. The products formed and their

Table 1. Chlorination of *p*-cresol (1a) with molecular chlorine. Effects of amount of chlorine, solvent, temperature and added catalyst on product distribution.<sup>a</sup>

Exp. No.	Molar ratio (Cl <sub>2</sub> : <i>p</i> -cresol)	Solvent	Temp. (°C)	Catalyst (mol) <sup>b</sup>	Products and yields (%)						Ratio dienones—phenols (2a + 8 + 5a + 7a) / (3a + 6a)
					2a	8	5a	7a	3a	6a	
1	1.0	DCM <sup>c</sup>	18	—	22	0	0	0	78	0	0.28
2	1.0	DCM	0	—	27	0	0	0	73	0	0.37
3	1.2	DCM	–40	—	8	10	14	0	26	42	0.47
3	1.5	DCM	–40	—	2	12	26	0	20	40	0.67
4	1.9	DCM	–40	—	0	21	29	0	6	44	1.0
5	2.1	DCM	–40	—	0	18	34	0	0	48	1.1
6	4.0	DCM	–40	—	0	18	35	0	0	47	1.1
7	8.0	DCM	–40	—	0	17	27	6	0	50	1.0
8	2.9	DCM	0	—	0	18	36	0	0	46	1.2
9	2.9	DCM	–20	—	0	19	31	0	0	50	1.0
10	2.9	DCM	–35	—	0	20	35	0	0	45	1.2
11	1.0	DMF <sup>d</sup>	–40	—	24	0	0	0	76	0	0.32
12	1.0	DMF	–20	—	27	0	0	0	73	0	0.37
13	2.0	DMF	–40	—	27	0	16	0	23	24	0.75
14	2.0	DMF	20	—	23	0	24	3	7	43	1.0
15	2.9	DMF	–20	—	22	0	22	56	0	0	
16	9.0	DMF	–20	—	20	0	30	50	0	0	
17	1.0	CS <sub>2</sub>	19	—	0	0	0	0	>95		
18	1.0	CS <sub>2</sub>	–40	—	5	0	0	0	95		0.05
19	1.0	DCM	–40	BF <sub>3</sub> OEt <sub>2</sub> (1)	25	0	0	0	75		0.33
20	1.0	DCM	–40	BF <sub>3</sub> OEt <sub>2</sub> (2)	35	0	0	0	65		0.54
21	1.0	DCM	–20	BF <sub>3</sub> OEt <sub>2</sub> (2)	34	0	0	0	66		0.52
22	1.0	DCM	20	BF <sub>3</sub> OEt <sub>2</sub> (2)	36	0	0	0	64		0.56
23	1.0	DCM	–40	BF <sub>3</sub> OEt <sub>2</sub> (3)	28	0	0	0	72		0.39
24	1.0	DCM	0	TiCl <sub>4</sub> (0.1)	25	0	0	0	75		0.33
25	1.0	DCM	0	TiCl <sub>4</sub> (0.25)	34	0	0	0	66		0.42
26	1.0	DCM	15	TiCl <sub>4</sub> (0.25)	28	0	0	0	72		0.39
27	1.0	DCM	0	TiCl <sub>4</sub> (0.5)	39	0	0	0	61		0.64
28	1.0	DCM	0	TiCl <sub>4</sub> (1.0)	35	0	0	0	65		0.54
29	1.0	DCM	0	TiCl <sub>4</sub> (2.0)	35	0	0	0	65		0.54
30	1.0	DCM	22	CF <sub>3</sub> COOH (5)	26	0	0	0	74		0.32
31	1.0	DCM	22	CF <sub>3</sub> SO <sub>3</sub> H (1)	20	0	0	0	80		0.25
32	1.0	CS <sub>2</sub>	–20	TiCl <sub>4</sub> (0.5)	31	0	0	0	69		0.45
33	1.0	CS <sub>2</sub>	0	TiCl <sub>4</sub> (1.0)	24	0	23	0	53		0.89

<sup>a</sup> The yields were determined from the NMR spectrum of the crude product mixture (for details see Experimental).  
<sup>b</sup> Molar ratio between *p*-cresol and the catalyst. <sup>c</sup> DCM = dichloromethane. <sup>d</sup> DMF = dimethyl formamide.



Scheme 1.

formation paths are shown in Scheme 1. As can be seen, the reaction temperature is of little importance whereas the other variables are of great importance. Addition of one mol of chlorine per mol of *p*-cresol always gives the highest yield of **2a**, as *p*-cresol turns out to be far more reactive towards chlorine than any of the products in Scheme 1. As long as *p*-cresol is present, the formations of **2a** and **3a** are the only reactions occurring. If more than one mol of chlorine is added, all the other reactions in Scheme 1 begin to take place. That is, addition of  $\text{Cl}_2$  to **2a** to give 2,3,4-trichloro-4-methylcyclohex-5-enone (**8**), chlorination of **3** to give a mixture of 2,4-dichloro-4-methylcyclohexa-2,5-dienone (**5a**) and 2,6-dichloro-*p*-cresol (**6a**), and finally chlorination of **6a** to give 2,4,6-trichloro-4-methylcyclohexa-2,5-dienone (**7a**) [NMR indicates that the addition of chlorine to **2a** is stereospecific, and only the *trans*- or the *cis*-3,4-dichloro isomer is formed.] That product formation actually occurs as shown in Scheme 1 was confirmed by reacting pure **2a**, **3a**, **5a** and **6a** with chlorine in DCM. On standing, **8** eliminates hydrogen chloride to give **5a** and exhaustive chlorination of *p*-cresol in either DCM or DMF (no catalyst added) eventually gives a 1:1 mixture of the dienones **5a** and **7a**.

In both DCM and DMF **2a** and **3a** are formed in

approximately a 1:3 ratio on chlorination with one mol of chlorine. However, in DMF the addition of chlorine to **2a** does not occur, probably because of the buffering effect of DMF which diminishes the acidity of the HCl catalyst formed in the chlorination. In  $\text{CS}_2$  essentially only ortho chlorination occurs. Addition of trifluoroacetic acid (TFA) or trifluoromethane sulfonic acid (TFMS) does not affect the yield of **2a**, whereas boron trifluoride etherate, and especially titanium tetrachloride, gives a marked increase of the yield of **2a** (exps. 22 and 27). At least two mols of boron trifluoride etherate and at least half a mol of titanium tetrachloride must be added to obtain the maximum yield of **2a**. This indicates that the actual species being chlorinated is a *p*-cresol-metal halide complex, where the metal halide is attached to the phenolic hydroxy group and thereby causes steric hindrance to ortho-chlorination. Changes of the electron density in the benzenoid ring caused by the increased electrophilicity of the oxygen substituent might also be important.

The results of chlorination of 2,4-dimethylphenol (**1b**), 3,4-dimethylphenol (**1c**), 2,4,5-trimethylphenol (**1d**), 2,4,6-trimethylphenol (**1e**), and the chlorinated phenols, **3a**, **6a**, **3b-d** and **6c** (formed in the chlorination of the phenols **1a-d**) are given in Table 2. No attempts to study the effect of added catalyst or solvent were made. The 2,6-substituted *p*-cresol derivatives, with the exception of 2,4,6-trimethylphenol (**1e**), all give quantitative yields of the cor-

Table 2. Chlorination of 2,4-dimethylphenol (*1b*), 3,4-dimethylphenol (*1c*), 2,4,5-trimethylphenol (*1d*), 2,4,6-trimethylphenol (*1e*), 4-chloro-4-methylcyclohexa-2,5-dienone (*2a*), 2-chloro-*p*-cresol (*3a*), 2,6-dichloro-*p*-cresol (*6a*), 6-chloro-2,4-dimethylphenol (*3b*), 2-chloro-3,4-dimethylphenol (*3c*), 2,6-dichloro-3,4-dimethylphenol (*6c*), and 6-chloro-2,4,5-trimethylphenol (*3d*) with molecular chlorine in DCM.<sup>a</sup>

Substrate	Products and yields (%)	Ratio dienones – chlorophenols
<i>1b</i>	<i>2b</i> (11); <i>5b</i> (16); <i>3b</i> (73)	0.27
<i>1c</i>	<i>2c</i> (47); <i>7c</i> (28); <i>3c</i> (5); <i>5c</i> (20)	3.0
<i>1d</i>	<i>2d</i> (67); <i>5d</i> (11); <i>3d</i> (22)	3.5
<i>1e</i>	<i>2e</i> (65); <i>4</i> (35)	---
<i>2a</i>	<i>8</i> (quant.)	---
<i>3a</i>	<i>5a</i> (45); <i>6a</i> (55)	0.8
<i>6a</i>	<i>7</i> (quant.)	---
<i>3b</i>	<i>5b</i> (quant.)	---
<i>3c</i>	<i>6c</i> (quant.)	---
<i>6c</i>	<i>7c</i> (quant.)	---
<i>3d</i>	<i>5d</i> (quant.)	---

<sup>a</sup> All experiments were carried out at 20 °C with addition of one mol of Cl<sub>2</sub> per mol of substrate. The conversions were 100% and the reaction time 20 min in all cases. The yields were determined from the NMR spectrum of the crude product (for details see Experimental).

responding 4-chlorodienones. With *1e* a mixture of the chlorodienone *2e* and 3-chloro-2,4,6-trimethylphenol (*4*) was obtained. The latter compound is probably formed by acid catalysed dienone-phenol rearrangement of *2e*. Protonation of *2e* gives a carbonium ion similar to *19c* (a hydroxy group instead of the methoxy group) in which chlorine migrates from C-4 to C-3. This rearrangement was not observed for any other chlorodienone in the chlorination experiments described in Table 2. However, the chlorodienones *2a–d*, *5a–b*, and *5c* all underwent the dienone-phenol rearrange-

ment to the corresponding 3-chlorinated phenols by treatment with TFMS in DCM.<sup>4</sup>

In our previous communication<sup>1</sup> we showed that the chlorodienone *2c* can readily be transformed to the corresponding 4-hydroxy-, 4-methoxy-, or 4-acetoxy-4-methylcyclohexa-2,5-dienones by silver catalysed solvolysis in presence of water, methanol, or acetic acid – sodium acetate. In our continued investigation we discovered that *2a* on standing in pure methanol rearranges to 2,4-dimethoxytoluene (*9a*). In other words chlorination of *p*-cresol with molecular chlorine in DCM followed by metha-

Table 3. Reaction of the 4-chloro-4-methylcyclohexa-2,5-dienone derivatives, *2a–e*, *5a–b*, *5d*, and *7c* with methanol.<sup>a</sup>

Dienone	Reaction time (h)	Products and yields <sup>b</sup> (%)
<i>2a</i>	8	2,4-dimethoxytoluene ( <i>9a</i> , quant.)
<i>2b</i>	24	1,3-dimethoxy-4,6-dimethylbenzene ( <i>9b</i> , quant.)
<i>2c</i>	8	1,3-dimethoxy-5,6-dimethylbenzene ( <i>9c</i> , quant.)
<i>2d</i>	24	5-methoxy-2,3-dimethylbenzyl methyl ether ( <i>11</i> , quant.)
<i>2e</i>	168	4-methoxy-2,4,6-trimethyl cyclohexa-2,5-dienone ( <i>12e</i> , 42); 3-chloro-2,4,6-trimethyl phenol ( <i>4</i> , 58)
<i>5a</i>	24	5-chloro-2,4-dimethoxytoluene ( <i>10a</i> , quant.)
<i>5b</i>	48	6-chloro-4-methoxy-2,4-dimethylcyclohexa-2,5-dienone ( <i>13b</i> , quant.)
<i>5b</i>	168	6-chloro-4-methoxy-2,4,5-trimethylcyclohexa-2,5-dienone ( <i>13d</i> , quant.)
<i>7a</i>	168	2,6-dichloro-4-methoxy-4-methylcyclohexa-2,5-dienone ( <i>14a</i> , quant.)
<i>7c</i>	168	2,6-dichloro-4-methoxy-3,4-dimethylcyclohexa-2,5-dienone ( <i>14c</i> , quant.)

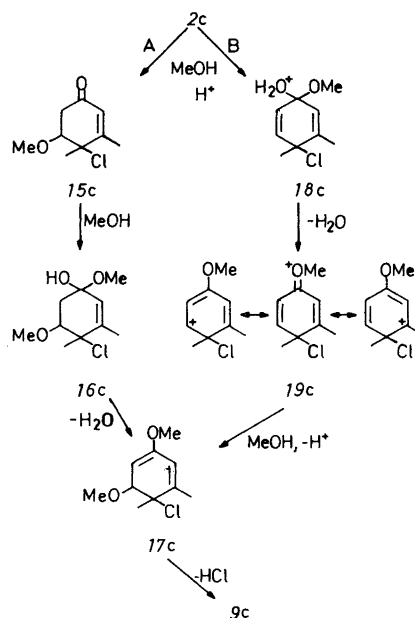
<sup>a</sup> The dienone was simply dissolved in pure methanol (large excess) and left at room temperature for the length of time indicated. <sup>b</sup> The yields were determined from the NMR spectrum of the crude product.

nolysis affords a facile synthetic method for the introduction of an oxygen in the 3-position of *p*-cresol, a transformation which otherwise requires several steps and cumbersome isomer separations. Previously<sup>5</sup> 2,4-dimethoxytoluene has been prepared in very low yield (3.6 %) by treatment of 4-hydroxy-4-methylcyclohexa-2,5-dienone with methanol containing approximately 2 % by weight of concentrated sulfuric acid. The major products were 2-methoxy-5-hydroxytoluene (54.7 %) and 2,4,4'-trimethoxy-5,2'-dimethylbiphenyl (24.3 %). The mechanism for the formation of these products will be discussed later.

In order to test the generality of our methoxylation reaction, all of the 4-chloro-4-methylcyclohexa-2,5-dienones prepared in this study (Tables 1 and 2) were subjected to methanolysis. The results are shown in Table 3. 1,3-Dimethoxy-4,6-dimethylbenzene (*9b*) has also been obtained in almost quantitative yield from 4-hydroxy-2,4-dimethylcyclohexa-2,5-dienone (which most conveniently is prepared by electrochemical oxidation of 2,4-dimethylphenol<sup>7</sup>) by treatment with methanol containing either concentrated sulfuric acid (4 %) or hydrogen chloride (2 %).<sup>6</sup> In this study<sup>6</sup> it was also shown that no *9b* was formed if the methanolysis was carried out in a 1:2 (vol/vol) mixture of concentrated sulfuric acid and methanol. In the latter case only 4-methoxy-3,6-dimethylphenol and dimers were obtained. From Table 3 it can be seen that 2,6-substituted chlorodienones do not give any dimethoxyaromatics on methanolysis. The only reaction observed is substitution of the 4-chlorine with a methoxy group (*5b*, *7a* and *7c-d*) or rearrangement to the 3-chlorophenol derivative (*2e*). Furthermore we can see that a chlorine or methyl substituent deactivates the adjacent 3- or 5-position and thus prevents methoxylation in this position. Finally the results of the methanolysis of *2a-b*, *2d*, *5a*, and *5c-d* show that migration of chlorine is only prevented by an adjacent chlorine substituent not by a methyl substituent.

The methanolysis of *2d* gives only side chain methoxylation and no ring methoxylation. This amounts to a selective oxidation of the least reactive of the three methyl groups in *2d*. The benzylic methoxy group in *11* can easily be oxidised further to an aldehyde or carboxylic acid function. It should be noted that only ring methoxylation (in the 3-position) occurs by methanolysis of the chlorodienone *2c*.

Two slightly different mechanisms can be envi-

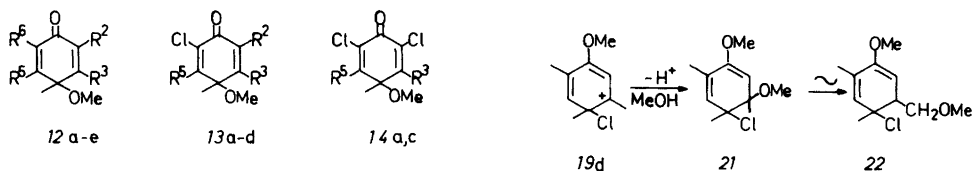


Scheme 2.

sioned for the formation of the dimethoxyaromatics (*9* and *11*) by methanolysis of the 4-chloro-4-methylcyclohexa-2,5-dienones *2a-d* and *4a*. In the first (mechanism A in Scheme 2), the initial reaction is either 1,2-addition of methanol to one of the double bonds of the cyclohexadienone ring or 1,4-addition of methanol to the  $\alpha,\beta$ -unsaturated carbonyl system of the cyclohexadienone followed by enol-keton tautomerisation. In both cases the product formed is *15c*. In Scheme 2 compound *2c* is used as an example. *2a* and *2b* react similarly. The intermediate *15c* then adds methanol to the carbonyl double bond with formation of the hemiketal *16c*, which eliminates water (to *17c*) and hydrogen chloride to finally give the 1,3-dimethoxybenzene derivative *9c*. It should be noted that the order of the two first steps in mechanism A could be reversed.

In the other mechanism (B in Scheme 2), formation of the protonated hemiketal *18c* is assumed to be the first step. By elimination of water from *18c*, the carbonium ion *19c* is formed. From the three resonance structures shown in Scheme 2, it can be seen that *19c* should react with methanol in either the 3- or the 5-position of the ring. From our experimental data we know that methoxylation of *2c* only occurs in the 5-position although the 3-methyl substituent should stabilise a positive charge at

C-3. This can be explained by a rapid irreversible elimination of hydrogen chloride from the intermediate *17c*. An intermediate formed by nucleophilic attack of methanol on the 3-position of *19c* cannot directly eliminate hydrogen chloride. The methanolysis of *2d* (see Scheme 3) indicates that such an intermediate undergoes an intramolecular rearrangement/elimination reaction leading eventually to a side chain methoxylated aromatic compound. This reaction is expected to be slower than the direct elimination/aromatisation reaction observed for *2c*. The present data does not allow



any conclusions concerning the relative importance of mechanisms A and B.

The chlorodienone *2d* reacts with methanol to give the side-chain methoxylated product *11*. Also in this case we believe that a mechanism similar to A or B in Scheme 2 is in operation. In this case mechanism A, however, involves addition of methanol to the tautomeric form of *2d* with an exocyclic double bond (see Scheme 3). The carbonium ion path (B) is also shown in Scheme 3. The initial formation of the hemiketal and the subsequent elimination of methanol to form the carbonium ion *19d* are not shown. The rearrangement/elimination reaction leading from *21* to *11* is shown as a stepwise sequence in Scheme 3. However, a concerted mechanism is probably in operation.

The substituent effects described above on the methanolysis reaction of the 4-chloro-4-methylcyclohexa-2,5-dienones are very well explained by both mechanism A or B in Scheme 2 or 3, since both the addition of methanol to a double bond (or  $\alpha,\beta$ -unsaturated carbonyl system) of the cyclohexa-2,5-dienone or the exocyclic double bond of the tautomeric form of *2d* (mechanism A) and the reactivity of the intermediate carbonium ion (*19c* or *19d*) towards methanol should be strongly affected by steric hindrance from the substituents of the cyclohexadienone ring and by changes in electron density caused by electron withdrawing substituents (chlorine).

The 2,6-substituted 4-chloro-4-methylcyclohexa-2,5-dienones (*2e*, *5b*, *5d*, *7a* and *7c*) yield 4-methoxy-4-methylcyclohexa-2,5-dienones (*12e*, *13b*, *13d*, *14a*

Scheme 3.

and *14c*) on treatment with methanol (Table 3). One might therefore suspect that 4-methoxydienones could be intermediates in the methanolysis of the 4-chlorodienones *2a-d* and *4a*. However, the 4-methoxydienones *12a-d* and *13a* obtained by silver ion assisted methanolysis<sup>2</sup> of the corresponding 4-chlorodienones were all stable in pure methanol. Treatment of these 4-methoxydienones with methanol containing concentrated sulfuric acid (2%) resulted in the formation of both 1,3-dimethoxy- and 1,4-dimethoxyaromatics and dimeric products as would have been expected from the previous studies of the corresponding 4-hydroxydienones.<sup>5,6</sup> The 1,3-dimethoxyaromatics obtained by acid catalysed methanolysis of the 4-methoxydienones are probably formed by a mechanism similar to A or B (Scheme 2 or 3). However, the formation of the 1,4-dimethoxyaromatics (and the formation of the hydroquinone monomethyl ethers from 4-hydroxydienones<sup>5,6</sup>) must involve migration of the 4-methyl group in a carbonium such as *19* (with a methoxy or a hydroxy group instead of the 4-chloro substituent). This indicates that in presence of strong acid (>2%) mechanism B is most important. Mechanism B also explains very well that strong acid in large excess suppresses the formation of the 1,3-dimethoxyaromatics from both the 4-methoxy- and the 4-hydroxydienones<sup>5,6</sup> as the formation of *17c* from *19c* (Scheme 2) involves a de-

Table 4. Yields of dimethoxy aromatic compounds obtained from the *p*-cresol derivatives 1*a*–*e* and 3*a* by chlorination with molecular chlorine in DCM followed by methanolysis (method A) and by direct chlorination with molecular chlorine in methanol (method B).<sup>a</sup>

Phenol	Products and yields (%) by method A <sup>b</sup>	Products and yields (%) by method B <sup>b,c</sup>
1 <i>a</i> <sup>d</sup>	9 <i>a</i> (33)	9 <i>a</i> (16); 10 <i>a</i> (13)
1 <i>b</i>	9 <i>b</i> (16)	9 <i>b</i> (21)
1 <i>c</i>	9 <i>c</i> (36)	9 <i>c</i> (28)
1 <i>d</i>	11 (51)	11 (53)
1 <i>e</i>	None (see Table 2)	None <sup>e</sup>
3 <i>a</i>	10 <i>a</i> (43)	10 <i>a</i> (40)

<sup>a</sup> Preparative scale experiments. In all cases 0.2 mol of chlorine dissolved in DCM was added to 0.2 mol of the phenol dissolved either in DCM (method A) or in methanol (method B). Chlorination of the chlorophenols 3*c*–*d*, 6*a*, or 6*c* gave the corresponding chlorodienones (see Table 2) by method A and mixtures of chlorodienones and the corresponding methoxydienones by method B (see Table 3). <sup>b</sup> The yields refer to products isolated and purified. <sup>c</sup> The chlorination in methanol is less selective than that in DCM, and all possible chlorination products (see Tables 1 and 2) as well as the product of reaction of methanol with the various chlorodienones (see Table 3) are observed. <sup>d</sup> Titanium tetrachloride was added as catalyst (0.5 mol). <sup>e</sup> The products were 12*e* (28%) and 4 (68%).

protonation step. At high acid concentration methyl group migration occurs with final formation of a hydroquinone derivative.

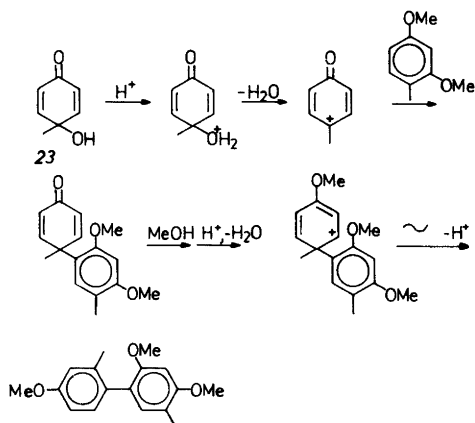
In conclusion, 4-methoxydienones can be excluded as intermediates in the methanolysis of the 4-chlorodienones described here (Table 3). Furthermore the much higher reactivity of the 4-chlorodienones compared to the 4-hydroxy- or 4-methoxydienones and the absence of methyl group migration in the methanolysis of 4-chlorodienones (at high acid concentrations chlorine migration actually occurs) is remarkable.

*Preparative experiments.* In a series of preparative scale experiments aiming at the synthesis of the dimethoxyaromatics 9*a*–*c* and 11, we discovered that isolation and purification of the 4-chlorodienones (2*a*–*d*) were not necessary. Directly after the chlorination a large excess of methanol was added to the reaction mixture and, when all of the 4-chlorodienone had reacted with methanol, the solvents were removed, the residue was dissolved in ether and extracted with 1 M sodium hydroxide, which removed all of the phenolic compounds from the product. Left in the ether solution was almost pure 9*a*–*c* or 11 (see Table 4). We also discovered that the dimethoxy compounds 9*a*–*c* and 11 are formed directly from the corresponding phenols 1*a*–*d* when the chlorination is carried out in pure methanol at low temperature (Table 4). None of the 4-chlorodienones 2*a*–*d* or 5*a*, which give dimethoxyaromatics on methanolysis, were observed after the chlorination in methanol. However, all

the other 4-chlorodienones (5*b*, 5*d*–*e*, 7*a* and 7*c*), the chloro compound 4, and to some extent also the 4-methoxydienones 12*e*, 13*b*, 13*d*, 14*a* and 14*c* were observed, showing that the chlorination in methanol is less selective than that in DCM. Although the 4-chlorodienones 2*a*–*d* could not be observed on chlorination in methanol, we still believe that they are intermediates. However, the hydrogen chloride formed in the chlorination reaction catalyzes the addition of methanol to the double bond of the cyclohexa-2,5-dienone and the further ketalisation (see Schemes 2 and 3).

The yields of dimethoxy aromatics from the various *p*-cresol derivatives by the method described in this study are quite low. However, the low yields are compensated for by the convenience of the method and the simplicity of the isolation procedure. Furthermore, our attempts to improve the yields by adding different Friedel-Crafts catalysts (Table 1) indicate that improvements in yield could be achieved in this way.

Another interesting development would be to treat the 4-chlorodienones with other nucleophiles than methanol either in the presence of acid or silver ions. In the latter case the 4-chlorodienone is converted to a phenoxonium ion which reacts with the nucleophile to give a new dienone with the nucleophile in the 4-position. The 2,4,4'-trimethoxy-5,2'-dimethylbiphenyl obtained by Bamberger<sup>5</sup> on methanolysis of 23 is probably formed in a sequence like that in Scheme 4. Therefore silver ion catalysed reaction of 4-chloro-4-methylcyclohexa-2,5-dienones



Scheme 4.

with a phenol ether in presence of acid should be a feasible synthesis of unsymmetrical biphenyls.

## EXPERIMENTAL

The phenols *1a–e* were commercial products. The chlorophenols *3a–d*, *6c* and *6d* were prepared by chlorination of *1a–d*, *3a* and *3c* in carbon disulfide with one mol of chlorine and purified as described in the literature. The NMR spectra were recorded with a 60 MHz instrument in deuteriochloroform solutions with Me<sub>4</sub>Si as internal standard.

*Chlorination of the phenols 1a–d, 3a–d, 6a and 6c. Analytical experiments. General.* The phenol (0.01 mol) was dissolved in DCM, DMF or CS<sub>2</sub>, 10 ml, and when applicable the Friedel-Crafts catalyst was added and the resulting mixture cooled to the reaction temperature indicated in Tables 1 and 2. Chlorine dissolved in DCM (1 M solution) at 0°C was then added rapidly with stirring. The amount of chlorine added is shown in Tables 1 and 2. The mode of addition of the molecular chlorine did not affect the product distribution: whether chlorine was added in gaseous form or in solution, slowly or rapidly or even if the addition was reversed, lead to no change in the products. After the chlorination the solvent was removed by distillation at reduced pressure (50°C) and the residue was analysed by NMR. The different products in the reaction mixture were identified by comparison with the NMR of the pure compounds obtained as described below. The results of the analytical chlorination experiments are given in Tables 1 and 2.

*Synthesis of the 4-chloro-4-methyl-cyclohexa-2,5-dienones 2a–e, 5a–b, 5d, 7a, and 7c. General.* The

chlorination was carried out at room temperature using one mol of chlorine as described above. When DCM was used as a solvent all phenolic compounds were extracted from the reaction mixture with a phosphate buffer (pH 12, 0.5 M, made from Na<sub>3</sub>PO<sub>4</sub> and half an equivalent of HCl). Evaporation of the DCM yielded the crude 4-chlorodienone which was further purified by chromatography on silica gel (DCM eluent). The yields of pure 4-chlorodienones in general were about 5% lower than the NMR yields reported in Tables 1 and 2. The physical and spectroscopic data of the 4-chlorodienones *2a–c*, *2e* and *5a*, have been reported previously (Refs. 1 and 3) and are in accordance with those obtained in this study.

*2,3,4-Trichloro-4-methylcyclohexa-5-enone (8).* Obtained by addition of 1 mol of chlorine to *2a* in DCM at room temperature. Liquid. *M*<sup>+</sup> 212 *m/e*. NMR δ 7.10 (H5, d, *J* = 10 Hz), 6.05 (H6, d, *J* = 10 Hz), 4.55 (H2, H3, m), 1.86 (3H, s, Me-4) ppm.

*4,6-Dichloro-2,4-dimethylcyclohexa-2,5-dienone (5b).* Obtained from chlorination of *3b* with one mol of chlorine in DCM as described above. Liquid. *M*<sup>+</sup> 190 *m/e*. NMR δ 7.17 (H5, d, *J* = 3 Hz), 6.82 (H3, m), 1.92 (Me-2, bs), and 1.82 (Me-4, s) ppm.

*2,4,6-Trichloro-4-methylcyclohexa-2,5-dienone (7a).* Obtained by chlorination of *6a* with one mol of chlorine in DCM as described above. M.p. 53–54°C. *M*<sup>+</sup> 210 *m/e*. NMR δ 7.18 (2H, s) and 1.93 (3H, s) ppm.

*4,6-Dichloro-2,4,5-trimethylcyclohexa-2,5-dienone (5d).* Obtained by chlorination of *3d* as described above. M.p. 38–40°C. *M*<sup>+</sup> 204 *m/e*. NMR δ 6.83 (H3, bs), 2.28 (Me-5, s), 1.96 (Me-2, bs), and 1.83 (Me-4, s) ppm.

*2,4,6-Trichloro-3,4-dimethylcyclohexa-2,5-dienone (7c).* Obtained by chlorination of *6c* as described above. M.p. 47–48°C. *M*<sup>+</sup> 238 *m/e*. NMR δ 7.23 (H5, s), 2.40 (Me-3, s) and 1.87 (Me-4, s) ppm.

*4-Chloro-2,4,5-trimethylcyclohexa-2,5-dienone (2d).* Obtained by chlorination of *1d* as described above. Liquid. *M*<sup>+</sup> 170 *m/e*. NMR δ 6.80 (H3, bs), 6.10 (H6, bs), 2.13 (Me-5, s), 1.85 (Me-2, s), and 1.71 (Me-4, s) ppm.

*3-Chloro-2,4,6-trimethylphenyl (4).* *1e* was chlorinated with one mol of chlorine in DCM as described above. Analysis of the reaction mixture 15 min after the chlorine addition showed that *1e* had been converted to a 13:7 mixture of *2e* and *4*. The reaction mixture was left at room temperature for 24 h. During this period all of *2e* rearranged to *4* which could be isolated in quantitative yield by evaporation of the solvent. White needles, m.p. 81–83°C, Lit<sup>8</sup> 81–83°C *M*<sup>+</sup> 170 *m/e*. NMR δ 6.80 (H5, s), 4.58 (OH, s), 2.26 (6H, s), and 2.13 (3H, s) ppm.

*Methanolysis of the 4-chloro-4-methylcyclohexa-2,5-dienone derivatives. Analytical experiments. General.* The pure 4-chlorodienone (obtained as



described above) was dissolved in a 100-fold molar excess of methanol and left standing at room temperature until all of the 4-chlorodienone had reacted (NMR). Then the methanol was removed by distillation at 50°C and reduced pressure and the resulting product analysed by NMR. The different compounds in the product were identified by comparison with the NMR spectra of the pure compounds obtained as described below. The yields were determined from the integrated NMR spectra and are given together with reaction times in Table 3.

The products from methanolysis of the pure 4-chlorodienones were isolated from the reaction mixture either directly by recrystallisation from ether (crystalline compounds) or by chromatography on silica gel (DCM eluent). In this manner the following compounds were obtained:

*2,4-Dimethoxytoluene* (9). From methanolysis of 2a. Oil.  $M^+$  152 *m/e* NMR  $\delta$  7.00 (H<sub>6,d</sub>,  $J=9$  Hz), 6.45 (H<sub>3,H5,m</sub>), 3.80 (6H<sub>s</sub>), and 2.15 (3H<sub>s</sub>) ppm.

*1,3-Dimethoxy-4,6-dimethylbenzene* (9b). From methanolysis of 2b. M.p. 75–76°C (lit.<sup>6</sup> M.p. 76°C).  $M^+$  166 *m/e*. NMR  $\delta$  6.87 (H<sub>5,s</sub>), 6.43 (H<sub>2,s</sub>), 3.76 (6H<sub>s</sub>), and 2.10 (6H<sub>s</sub>) ppm.

*1,3-Dimethoxy-5,6-dimethylbenzene* (9c). From methanolysis of 2c. Oil; b.p. 117–118°C/11 mmHg (lit.<sup>9</sup> 117–118°C/11 mmHg).  $M^+$  152. NMR  $\delta$  6.32 (H<sub>2,H6,s</sub>), 3.77 (6H<sub>s</sub>), 2.22 (Me-5,s), and 2.06 (Me-4,s) ppm.

*5-Methoxy-2,3-dimethylbenzyl methyl ether* (11). From methanolysis of 2d. Oil;  $M^+$  166 *m/e*. NMR  $\delta$  6.87 (1H<sub>s</sub>), 6.83 (1H<sub>s</sub>), 4.37 (Ar-CH<sub>2</sub>-O-, s), 3.77 (Ar-CMe,s), 3.36 (-CH<sub>2</sub>-OMe,s) and 2.18 (6H<sub>s</sub>) ppm.

*4-Methoxy-2,4,6-trimethylcyclohexa-2,5-dienone* (22e). From methanolysis of 2e. M.p. 111.5–112°C (lit.<sup>7</sup> 111.5–112°C). Spectroscopic data has been published previously.<sup>7</sup>

*5-Chloro-2,4-dimethoxytoluene* (10a). From methanolysis of 5a. M.p. 74–75°C.  $M^+$  186 *m/e*. NMR  $\delta$  7.07 (H<sub>6,s</sub>), 6.47 (H<sub>3,s</sub>), 3.83 (3H<sub>s</sub>), 3.76 (3H<sub>s</sub>), and 2.12 (3H<sub>s</sub>) ppm.

*6-Chloro-4-methoxy-2,4-dimethylcyclohexa-2,5-dienon* (13b). From methanolysis of 5b. M.p. 138–140°C.  $M^+$  136 *m/e*. NMR  $\delta$  6.98 (H<sub>5,d</sub>,  $J=3$  Hz), 6.67 (H<sub>3,m</sub>), 3.20 (OMe,s), 1.97 (Me-2,bs), and 1.43 (Me-4,s) ppm.

*6-Chloro-4-methoxy-2,4,5-trimethylcyclohexa-2,5-dienone* (13d). From methanolysis of 5d. M.p. 118–120°C.  $M^+$  200 *m/e*. NMR  $\delta$  6.63 (H<sub>3,bs</sub>), 3.46 (OMe,s), 2.10 (Åe-5,s), 1.96 (Me-2, bs), and 1.40 (Me-4,s) ppm.

*2,6-Dichloro-4-methoxy-4-methylcyclohexa-2,5-dienone* (14a). From methanolysis of 7a. M.p. 161–162°C.  $M^+$  206 *m/e*. NMR  $\delta$  7.03 (H<sub>3,H5,s</sub>), 3.27 (OMe,s), and 1.50 (Me-4,s) ppm.

*2,6-Dichloro-4-methoxy-3,4-dimethylcyclohexa-2,5-dienone* (14c). From methanolysis of 7c. M.p. 148–150°C.  $M^+$  220 *m/e*. NMR  $\delta$  7.10 (H<sub>5,s</sub>), 3.13 (OMe,s), 2.17 (Me-3,s), and 1.50 (Me-4,s) ppm.

*Preparative experiments. Large scale synthesis of the dimethoxy aromatics 9a–b, 10a, and 11. Method A* (see Table 4). The starting phenol (1a–e or 3a, 0.2 mol) was dissolved at room temperature in DCM, 100 ml, and in the case of 1a TiCl<sub>4</sub>, 12 g, 0.5 mol, dissolved in DCM, 100 ml, was added before the chlorine, 0.2 mol, 14 g, dissolved in DCM, 200 ml. The chlorine solution was kept at 0°C and added in one batch with rapid stirring. Stirring was continued until all chlorine had been consumed. This required only a few minutes. Then methanol, 100 ml, was added and the solution was left at room temperature for 24 h after which the solvents were evaporated by distillation at reduced pressure and 50°C. The residue was dissolved in ether, 200 ml, and extracted with 1 M sodium hydroxide, 4 × 150 ml, and water, 3 × 100 ml. The residue obtained by evaporation of the ether solution was almost pure dimethoxy compound and was further purified by chromatography on silica gel (DCM eluent) or by recrystallisation from ether (see above).

*Method B* (see Table 4). The starting phenol was dissolved in methanol, 100 ml, and this solution was cooled to –60°C in a dry ice bath before the chlorination was carried out in the same way as described above. The reaction mixture was allowed to warm up to room temperature before the solvent was evaporated. The resulting residue was worked up as described under method A.

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