Regiospecific Chlorination of Aromatic Substrates using Donor–Acceptor and Hydrogen Bonding Interactions

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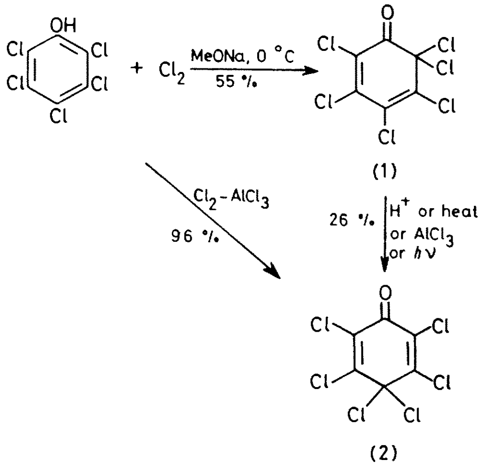
Summary The chlorination of aromatic substances has been achieved with good regioselectivity using 2,3,4,4,5,6-hexachlorocyclohexa-2,5-dien-1-one and 2,3,4,5,6,6-hexachlorocyclohexa-2,4-dien-1-one as chlorinating agents.

DURING the last few years numerous attempts have been made to halogenate selectively aromatic substrates. This has been done easily for iodination and bromination but very few selective methods have been described for chlorination,[1] an important process because of the number of interesting products which are chloroderivatives. The most important factor in determining the position taken by a second halogen atom in a monosubstituted aromatic system is the nature of the first substituent; its electronic and steric effects and its ability to solvate the electrophilic species. Here we propose a new strategy for solving this problem consisting of tailoring the chlorinating agent in such a way that the chlorine will be liberated in the right position.

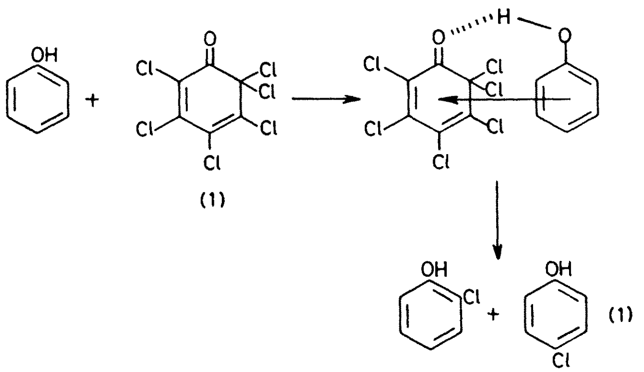
Aromatic rings, containing an electron releasing substituent such as a hydroxy or amino group (reactive but not selective substrates) interact in two ways with suitable reagents. If the reagent is a π acceptor a charge transfer complex is formed, with phenol or aniline acting as the π donor.[2] If the reagent contains a functional group which is a hydrogen bond acceptor then a hydrogen bond will form. For example benzoquinone forms a complex with *p*-chlorophenol in which the nuclei are parallel and the oxo and the hydroxy groups are opposite each other.[3]

In the literature numerous chlorinated cyclohexadienones have been described which can act as chlorinating agents. In the presence of phenols they can interact in two ways as described above. These cyclohexadienones may be synthesized easily by reaction of a suitable phenol with chlorine followed by isomerisation (Scheme).[4]

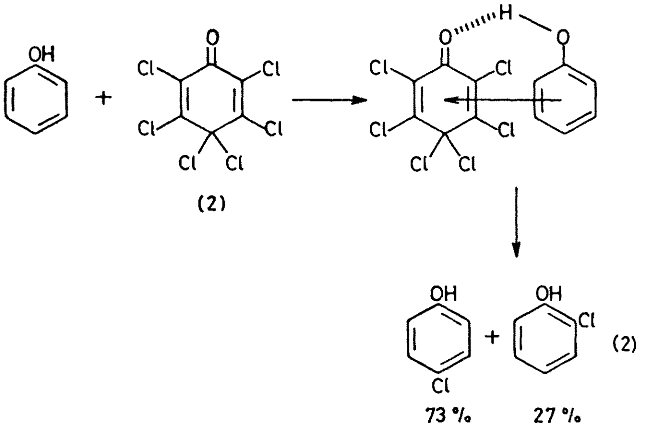


SCHEME

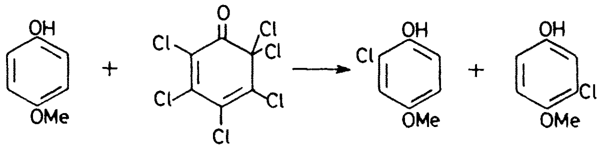
We have found that under the right conditions it is possible to chlorinate the phenol with good regiospecificity by using a suitable cyclohexadienone. For example, when



an equimolecular mixture of phenol and 2,3,4,5,6,6-hexachlorocyclohexa-2,4-dien-1-one (**1**) was irradiated in CCl_4 at −5 °C for 10 h with a 100 W Hanovia mercury lamp *o*-chlorophenol was obtained in 92% yield, with *p*-chlorophenol being obtained in only 8% yield [equation (1)].



The reaction of an equimolecular mixture of phenol and 2,3,4,4,5,6-hexachlorocyclohexa-2,5-dien-1-one (**2**) in dimethylformamide (DMF) for 72 h at 20 °C give a mixture of products, with *p*-chlorophenol predominating [equation (2)]. The chlorination of *o*-cresol with (**2**) in DMF gave 4-chloro-2-methylphenol (89.5%) with only traces of the 6-chloro-2-methylphenol. However, chlorination of *o*-cresol with (**1**) in CCl_4 containing 10% DMF gave 6-chloro-2-methylphenol (70%) with only 30% of 4-chloro-2-methylphenol when 73% of the *o*-cresol had reacted.



Selective chlorination *ortho* to a hydroxy group was accomplished in 4-methoxyphenol using (**1**) as a reagent, giving 93% of 2-chloro-4-methoxyphenol with a small amount of 3-chloro-4-methoxyphenol (2%) [equation (3)]. The direct chlorination of 4-methoxyphenol by chlorine leads to a mixture of mono-, di-, and tri-chloroderivatives and oxidation products.

These observations are particularly significant and show the potential of these reagents for the selective chlorination of convenient substrates.

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[1] P. B. D. de la Mare, 'Electrophilic Halogenation,' Cambridge University Press, 1976.

[2] R. Foster, 'Molecular Complexes,' Elek Science, London, 1973, vol. I and II.

[3] G. G. Shipley and S. C. Wallwork, *Acta Cryst.*, 1967, **22**, 593.

[4] L. Denivelle and R. Fort, *Bull. Soc. chim. France*, 1956, 1834.