

Novel highly selective catalytic oxychlorination of phenols

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The highly selective oxychlorination of various phenols catalyzed by CuCl_2 under mild conditions, in which chloride ions are used as chlorinating agents and dioxygen as a final oxidant, has been developed.

Chlorophenols are widely used in pharmaceutical, agricultural and dye industries for the production of various drugs, insecticides, herbicides, dyestuffs, etc.^{1,2} Common methods for their synthesis involve electrophilic aromatic halogenation reactions using various chlorinating agents such as chlorine,³ sulfonyl chloride (which readily dissociates into SO_2 and chlorine)^{4,5} and hypochlorites.⁶ An alternative pathway to chlorinated phenols is oxidative chlorination, which uses chloride ions as a chlorine source. Oxychlorination has many advantages compared to the conventional chlorination, such as fuller utilization of chlorine atoms and the use of low value and easy to handle chlorinating agents rather than more expensive and toxic ones, like chlorine. These reactions become especially attractive if dioxygen, the most abundant and cheapest oxidant, is involved.

Although the catalytic oxychlorination of ethylene with dioxygen has been developed into the important industrial synthesis of 1,2-dichloroethane,⁷ little was achieved with oxychlorination of aromatics. In most of the published works,^{8–11} peroxy compounds were used as oxidants, with complex mixtures of isomeric mono- and polychlorinated aromatics being usually obtained. Moreover, in substituted aromatics, the reactions are strongly complicated by the concomitant oxidation of side chains.

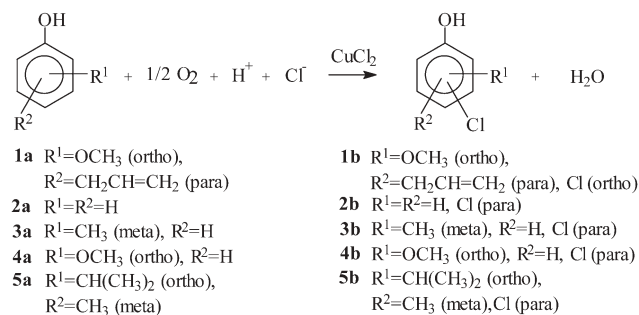
The present communication reports the remarkable activity of CuCl_2 to catalyze under mild conditions the oxychlorination of various phenols with dioxygen, affording monochlorinated products with high chemo- and regioselectivity. The presence of the hydroxy group attached to the aromatic nucleus was found essential for the reactivity of the aromatic substrate for oxychlorination, so that non-phenolic aromatics undergo no reaction at all in these systems. Thus, the method can be applied to perform a specific chlorination of phenols present in a mixture of various aromatic compounds.

We have recently been involved in palladium catalyzed aerobic oxidations of naturally occurring olefins.^{12–14} Studying the PdCl_2 – CuCl_2 catalyzed oxidation of eugenol (**1a**), which is an allylbenzene easily available from biomass, we have observed that its solutions in acetic acid containing CuCl_2 and LiCl readily consume dioxygen even in the absence of palladium. Gas chromatography (GC) showed the formation of only one product, which was isolated from the reaction solution by column chromatography and

completely characterized by GC/MS (Hewlett-Packard MSD 5890/Series II, 70 eV) and ^1H and ^{13}C -NMR (Bruker DRX-400, tetramethylsilane, CDCl_3 , COSY, HMQC, DEPT and NOESY experiments). The obtained data revealed that under the conditions used, a selective chlorination of the aromatic nucleus of eugenol occurred resulting in monochlorinated product **1b** with chlorine being in the *ortho*-position.

This oxidative transformation of eugenol formally consists of a nucleophilic substitution of aromatic hydrogen by Cl^- and a further oxidation of H^- by CuCl_2 , i.e. oxychlorination (Scheme 1). Reduced copper(I) species are readily re-oxidized back by dioxygen. Under optimized conditions at 80 °C and an oxygen pressure of 1 atm,[†] nearly complete conversion of eugenol occurred after a 6 h reaction (Table 1, run 1). The remarkable selectivity of this reaction should be mentioned: no traces of *meta*-isomer or polychlorinated products were observed, with chemo-selectivity being virtually 100%.

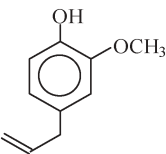
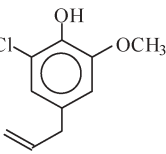
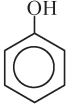
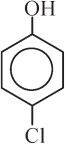
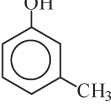
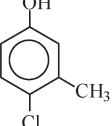
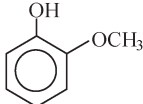
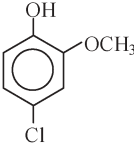
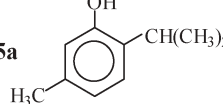
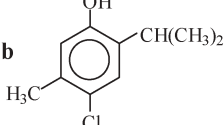
The reactivities of various aromatic compounds were examined under similar conditions. Some of these results are collected in Table 1. The reaction with phenol itself occurs much slower than that with eugenol resulting in a 93% conversion for 24 h (run 2). A high selectivity of 90% for *para*-chlorophenol **2b** has been obtained in this reaction under non-optimized conditions, with only small amounts of *ortho*-isomer being detected. On the other hand, phenols having at least one more electron donating group, i.e., *meta*-cresol **3a**, guaiacol **4a** and thymol **5a**, undergo the CuCl_2 catalyzed oxychlorination at much higher rates, like eugenol. Nearly complete conversions and excellent selectivities for *para*-chlorinated products were achieved in most of the reactions after 4–6 h (runs 3–5). Only in the case of guaiacol (run 4) have some secondary products been detected by GC, however at lower temperature (60 °C) selectivity increases to 97% at 82% conversion (run 6). Although these side products have not been fully identified yet, GC/MS analyses show that they contain no or only one chlorine atom, indicating that no polychlorination occurred.



Scheme 1

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Table 1 Oxychlorination of phenols catalyzed by CuCl₂^a

Run	Substrate (0.40 M)	Time (h)	Conversion (%)	Product	Selectivity (isolated yield) (%)
1	Eugenol 1a 	6	94	1b 	99 (82)
2	Phenol 2a 	24	93	2b 	90
3	<i>meta</i> -Cresol 3a 	6	90	3b 	99 (81)
4	Guaiacol 4a 	6	94	4b 	52
5	Thymol 5a 	4	92	5b 	99 (87)
6 ^b	Guaiacol 4a	7	82	4b	97

^a Conditions: solvent: acetic acid, [CuCl₂] = 0.05 M, [LiCl] = 0.80 M, 80 °C, O₂ (1 atm). Conversion and selectivity were determined by GC.
^b 60 °C.

As mentioned above, the *para*-isomers of monochlorinated products are exclusively formed from all studied phenols, except eugenol, in which the *para*-position is occupied by the allylic group. Although *ortho*-chlorination of eugenol occurs smoothly, no significant amounts of corresponding *ortho*-isomers are formed from substituted phenols having the *para*-position available. Also, no further *ortho*-chlorination of *para*-chlorophenols **3b–5b** has been observed even at longer reaction times. Thus, the presence of the electron withdrawing chlorine atom attached to aromatic nucleus in primarily formed products virtually suppresses their further chlorination.

The results obtained clearly demonstrate the generality of the catalyst in the *para*- or *ortho*-oxychlorination of phenol and electron-rich phenolic compounds. The catalytic system shows not only high regioselectivity but also a remarkable chemoselectivity for monochlorination. It is also important that no products of the oxidation of phenols are formed in detectable amounts.

Non-phenolic compounds examined in this reaction, both with electron withdrawing and with electron donating groups, *i.e.* anisole, nitrobenzene, toluene and safrol, undergo no transformation at all under the conditions used for oxychlorination of phenols. Thus, the method is highly substrate specific and could be applicable to the chlorination of phenols in mixtures with other aromatics.

In the absence of CuCl₂, no chlorination products are formed and no other reactions occur with phenols under the conditions shown in Table 1. The oxychlorination of eugenol is approximately first order in the catalyst concentration. Moreover, when CuCl₂ was substituted by CoCl₂, no reaction was observed. These results show the important and specific role of the copper catalyst.

It is known that most oxidative transformations of phenols catalyzed by copper complexes involve, as a key feature, the one-electron oxidation of phenolate by Cu(II) to the corresponding phenoxy radical.¹⁵ Thus, although the mechanism of copper catalyzed oxychlorination of phenols is not clear so far, it can be suggested that a free radical mechanism is likely to operate in these systems. Mechanistic aspects of this reaction are under investigation in our laboratory.

Preliminary studies show that the method can be extended to solvents other than acetic acid, such as water, methanol, acetonitrile, *etc.* In particular, performing the process in water offers not only important technological and environmental advantages, but also makes possible the use of sodium chloride as the chlorine source rather than the more expensive lithium chloride. We have found that the oxychlorination of eugenol **1a** in aqueous solutions of NaCl and CuCl₂ (cat.) results exclusively in monochlorinated product **1b**.

In summary, CuCl₂ efficiently catalyzes the oxychlorination of phenols under mild conditions in various solvents including water.

Chloride ions are used as the halogenating agent and dioxygen as the final oxidant. These novel reactions are relatively fast, specific for monochlorination and highly regioselective for *para*- or *ortho*-substitution. The method might be applied to the synthesis of chlorophenols, which are widely used in pharmaceutical, agricultural and dye industries.

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Notes and references

† The reactions were carried out in a stirred glass reactor and followed by measuring the dioxygen uptake and by gas chromatography using dodecane as an internal standard (Shimadzu 17 instrument, Carbowax 20 M capillary column, flame ionization detector). In a typical run, a solution of the aromatic compound, dodecane, CuCl₂ and LiCl in acetic acid was intensively stirred under oxygen at 80 °C for a specified time.

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