

Research Article

Highly Selective Synthesis of Chlorophenols under Microwave Irradiation

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Received 7 February 2016; Accepted 17 March 2016

Academic Editor: Stojan Stavber

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Oxychlorination of various phenols is finished in 60 minutes with high efficiency and perfect selectivity under microwave irradiation. These reactions adopt copper(II) chloride (CuCl_2) as the catalyst and hydrochloric acid as chlorine source instead of expensive and toxic ones. Oxychlorination of phenols substituted with electron donating groups (methyl, methoxyl, isopropyl, etc.) at *ortho*- and *meta*-positions is accomplished with higher conversion rates, lower reaction time, and excellent selectivity. A proposed reaction mechanism is deduced; one electron transfers from CuCl_2 to phenol followed by the formation of tautomeric radical that can be rapidly captured by chlorine atom and converts into *para*-substituted product.

1. Introduction

Chlorophenols are essential chemical intermediates in industry for the preparation of drugs, dyes, insecticides, herbicides, functional polymers, and so forth [1–3]. They are traditionally synthesized through electrophilic aromatic halogenations reactions [4], which are usually accompanied with the formation of byproducts including acetone and methylstyrene as well as high energy consumption [2]. Thus, it is necessary to develop green and effective method to produce these important materials.

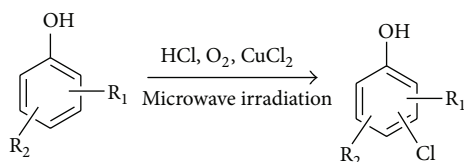
As an alternative method, direct oxidative chlorination catalyzed by CuCl_2 has been applied industrially to the conversion of ethylene into 1,2-dichloroethane [5], but there is very little literature reporting the oxychlorination of aromatics [6–8]. These reactions are usually carried out with poor selectivity and produce complex mixtures including mono- and poly-chloride substituted aromatic compounds [7, 8], which need further purification to get the desired products. Moreover, utilization of high value peroxy compounds such as *m*-chloroperbenzoic acid and potassium peroxomonosulfate is also an annoying problem [7, 8]. After the cheapest dioxygen was found as the oxidant, researches on oxychlorination of aromatics become interesting and

attractive. Menini and Gusevskaya reported the synthesis of chlorophenols catalyzed by CuCl_2 ; dioxygen was used as oxidant and lithium chloride was the chlorinating agent [9, 10], by which the oxychlorination reaction could be conducted under mild conditions, but some of the compounds were obtained with low selectivity and long reaction time [9, 10].

Microwave-promoted organic synthesis has been rapidly developed as it can dramatically shorten the reaction time and save the energy in a variety of synthetic transformations [11]. This paper describes an economically and easy to handle way to synthesize chlorophenols catalyzed by CuCl_2 under microwave irradiation. In this reaction, dioxygen is used as oxidant and hydrochloric acid as the chlorinating agent instead of expensive and toxic ones (Scheme 1).

2. Experimental

Chemical reagents were obtained from commercial sources and used without further purification. ¹H NMR spectra were recorded with a 400 MHz Bruker AV III spectrometer. HRMS spectra (negative) were finished on a Thermo Electron LTQ-Orbitrap XL spectrometer. All the reactions were performed on a MCR-3 microreactor (Beijing Xianghu Science and



SCHEME 1: Microwave-promoted oxychlorination of phenols.

Technology Development Co., Ltd., Beijing, China) and measured by a gas chromatography (GC) using a Shimadzu GC-2014C instrument.

2.1. General Methods. Phenols (78 mmol) and a catalytic amount of CuCl_2 (7.8 mmol) were dissolved in 100 mL of aqueous hydrochloric acid solution (6 mol/L), and the mixture was bubbled with dioxygen (22 mL/min). The reaction was performed on a microreactor at 50°C and measured by gas chromatography (GC). After GC showed the disappearance of the starting material, the reaction was extracted with dichloromethane (100 mL \times 2), and the organic layer was washed with water (50 mL \times 2) and fractionated to give the desired product.

^1H NMR and HRMS spectra can be seen in the Supplementary Materials available online at <http://dx.doi.org/10.1155/2016/2960414>.

Compound 1b: ^1H NMR (400 MHz, CDCl_3) δ 7.24–7.17 (m, 2H, Ph), 6.77–6.74 (m, 2H, Ph), 5.27 (s, 1H, OH); HRMS (ESI-TOF) m/z : calcd for $\text{C}_6\text{H}_4\text{ClO}$ $[\text{M} - \text{H}]^-$ 127.0029, found 126.9956.

Compound 2b: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.20 (s, 1H, OH), 6.95 (d, $J = 2.0$ Hz, 1H, Ph), 6.79–6.75 (m, 2H, Ph), 3.78 (s, 3H, OCH_3); HRMS (ESI-TOF) m/z : calcd for $\text{C}_7\text{H}_6\text{ClO}_2$ $[\text{M} - \text{H}]^-$ 157.0135, found 157.0056.

Compound 3b: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.55 (s, 1H, OH), 6.94–6.90 (m, 2H, Ph), 6.76 (dd, $J = 3.2, 8.8$ Hz, 1H, Ph), 3.69 (s, 3H, OCH_3); HRMS (ESI-TOF) m/z : calcd for $\text{C}_7\text{H}_6\text{ClO}_2$ $[\text{M} - \text{H}]^-$ 157.0135, found 157.0059.

Compound 4b: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.51 (s, 1H, OH), 7.16 (d, $J = 8.8$ Hz, 1H, Ph), 6.74 (d, $J = 2.4$ Hz, 1H, Ph), 6.62 (dd, $J = 2.8, 8.8$ Hz, 1H, Ph), 2.24 (s, 3H, CH_3); HRMS (ESI-TOF) m/z : calcd for $\text{C}_7\text{H}_6\text{ClO}$ $[\text{M} - \text{H}]^-$ 141.0185, found 141.0116.

Compound 5b: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 10.93 (s, 1H), 10.23 (s, 1H), 7.60 (d, $J = 2.8$ Hz, 1H, Ph), 7.54 (dd, $J = 2.8, 8.8$ Hz, 1H, Ph), 7.05 (d, $J = 8.8$ Hz, 1H, Ph); HRMS (ESI-TOF) m/z : calcd for $\text{C}_7\text{H}_4\text{ClO}_2$ $[\text{M} - \text{H}]^-$ 154.9978, found 154.9898.

Compound 6b: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.39 (s, 1H, OH), 7.04 (s, 1H, Ph), 6.72 (s, 1H, Ph), 3.15–3.12 (m, 1H, $\text{CH}(\text{CH}_3)_2$), 2.19 (s, 3H, CH_3), 1.12 (d, $J = 6.8$ Hz, 6H, $\text{CH}(\text{CH}_3)_2$); HRMS (ESI-TOF) m/z : calcd for $\text{C}_{10}\text{H}_{13}\text{ClO}$ $[\text{M} - \text{H}]^-$ 183.0655, found 183.0579.

Compound 7b: ^1H NMR (400 MHz, $\text{DMSO}-d_6$) δ 9.52 (s, 1H, OH), 7.10 (d, $J = 2.4$ Hz, 1H, Ph), 7.01 (dd, $J = 2.8, 8.4$ Hz, 1H, Ph), 6.78 (d, $J = 8.8$ Hz, 1H, Ph), 2.11 (s, 3H, CH_3); HRMS

(ESI-TOF) m/z : calcd for $\text{C}_7\text{H}_6\text{ClO}$ $[\text{M} - \text{H}]^-$ 141.0185, found 141.0107.

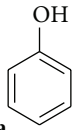
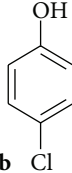
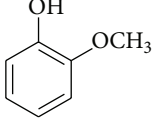
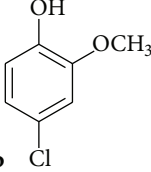
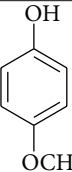
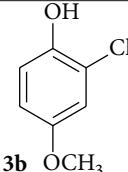
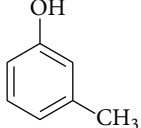
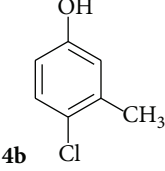
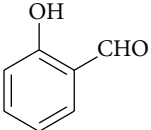
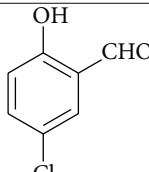
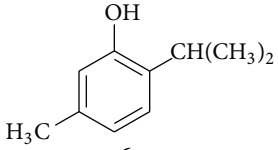
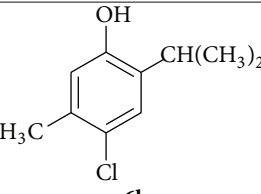
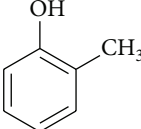
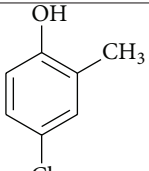
3. Results and Discussion

3.1. Oxychlorination of Phenols. Oxychlorination of various phenols was performed to investigate the reactivities (Table 1). Under microwave irradiation, 4-chlorophenol was prepared with high efficiency (93.4%) and perfect selectivity (96.6%), and the reaction was finished only in 60 minutes at 50°C (Entry 1) with minor amounts of *ortho*-substituted products being detected. Oxychlorination of phenols substituted by electron donating groups (methyl, methoxyl, isopropyl, etc.) at *ortho*- and *meta*-positions was accomplished with higher conversion rates, lower reaction time, and excellent selectivity. In particular, compound **6a**, simultaneously substituted by methyl and isopropyl groups at *ortho*- and *meta*-positions, completed the conversion with 100% efficiency and 99.8% selectivity (Entry 6). Furthermore, oxychlorination of *ortho*-substituted phenol with aldehyde group was still finished with high efficiency and excellent selectivity (Entry 5) but in 50 minutes. Substituting phenol with methoxyl group (**3a**) at *para*-position, the oxychlorination reaction occurred at *ortho*-position with lower conversion rate and poor selectivity due to the dual-orienting effect (Entry 3).

3.2. Proposed Reaction Mechanism. Different conditions were researched to investigate the proposed reaction mechanism in oxychlorination of phenol. As it is shown in Table 2, without addition of hydrochloric acid, there was no chlorination product detected in this reaction, and the chlorination efficiency was only 10.3% when hydrochloric acid was replaced with sulfuric acid, which indicated that hydrochloric acid was performed as chlorine source. As the catalyst, CuCl_2 played an essential role in chlorination reaction. In the absence of CuCl_2 , no product was formed and no other reactions were occurred, and replacement of CuCl_2 by lithium chloride still could not promote the reaction. Furthermore, the conversion rate was relatively low when the procedure was not bubbled with dioxygen, which proved its participation in oxidation.

A proposed reaction mechanism is depicted in Scheme 2. As conventional mechanism of phenol chlorination [9], one electron transfers from $\text{Cu}(\text{II})$ to phenoxy radical **B** via the complex **A** and simultaneously generates copper(I) chloride (CuCl). Then, radical **B** converts to the tautomeric structure **C**, followed by chlorination with CuCl_2 to form intermediate product **D** and CuCl . Tautomerization of **D** affords the desired product 4-chlorophenol, and CuCl generated in this reaction converts to CuCl_2 in the presence of hydrochloric acid and dioxygen. Our previous experiments revealed that insufficient concentration of $[\text{H}^+]$ caused the transformation of radical **C** to benzoquinone. Furthermore, major byproduct monitored in this reaction was 2-chlorophenol which was generated from tautomerization of radical **C** into **E**, and further conversions as the similar procedure to form 4-chlorophenol gave the *ortho*-substituted product. It seems that the key step of the reaction is the formation of radicals

TABLE I: Oxychlorination of phenols under microwave irradiation.

Entry	Substrate (0.78 M)	Product	Time (min)	Conversion (%)	Selectivity (%)
1	 1a	 1b	60	93.4	96.6
2	 2a	 2b	20	97.2	98.8
3	 3a	 3b	20	90.1	79.3
4	 4a	 4b	20	93.5	99.4
5	 5a	 5b	50	94.7	93.5
6	 6a	 6b	10	100	99.8
7	 7a	 7b	20	96.5	91.7

Conditions: microwave irradiation; solvent, aqueous hydrochloric acid solution (6 mol/L); reaction temperature (50°C). Conversion and selectivity were determined by GC.

C, and they are easily and rapidly captured by chlorine atoms compared with radicals E. Due to the high efficiency and perfect selectivity of this reaction, we deduce that microwave irradiation promoted the generation of radicals C, and their chlorination occurs faster than the traditional methods. And microwave irradiation seems to prevent the tautomerization of radicals C into E, which may be caused by the lower reaction temperature.

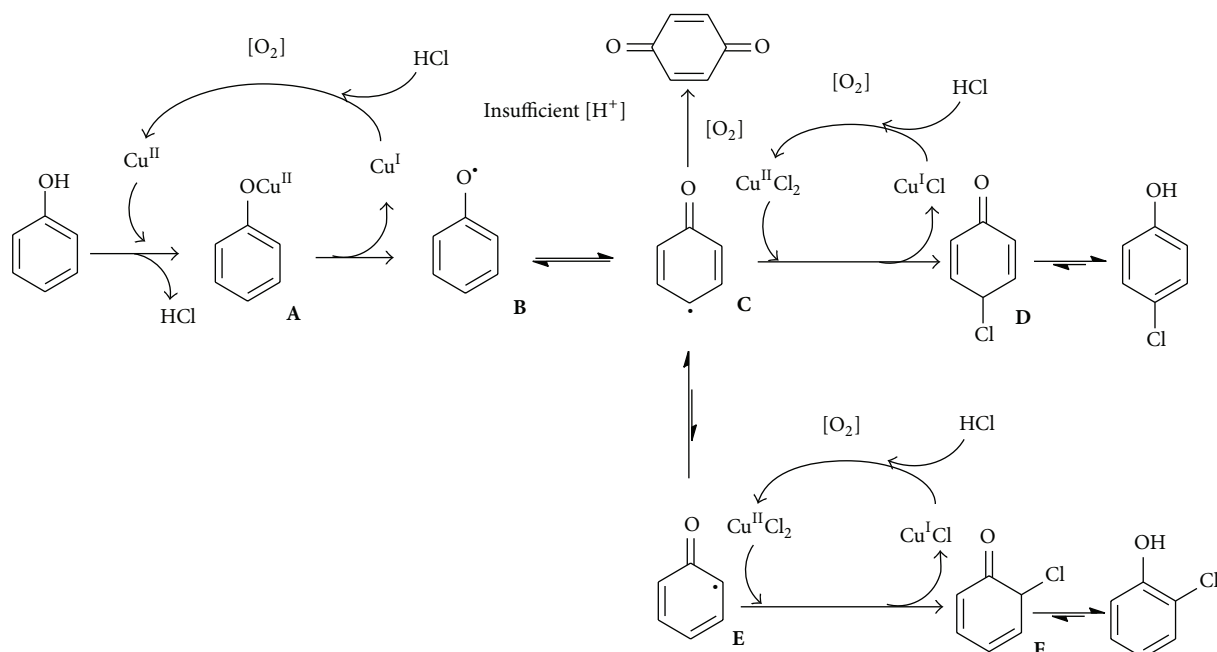
4. Conclusions

This paper describes the preparation of various chlorophenols promoted by microwave irradiation. Copper(II) chloride is used as the catalyst and hydrochloric acid as chlorine source instead of expensive and toxic ones. Using phenols substituted with electron donating groups at *ortho*- and *meta*-positions as substrates generates chlorophenols with

TABLE 2: Oxychlorination of phenol.

Entry	Acid	Catalyst	Dioxygen flow rate (mL/min)	Conversion (%)	Selectivity (%)
1	—	CuCl ₂ (0.1 eq.)	O ₂ (22 mL/min)	—	—
2	—	CuCl ₂ (2 eq.)	O ₂ (22 mL/min)	—	—
3	HCl (6 mol/L)	CuCl ₂ (0.1 eq.)	—	30.2	96.3
4	HCl (6 mol/L)	—	O ₂ (22 mL/min)	—	—
5	HCl (6 mol/L)	CuCl ₂ (0.1 eq.)	O ₂ (22 mL/min)	93.4	96.6
6	HCl (6 mol/L)	CuCl ₂ (2 eq.)	O ₂ (22 mL/min)	94.1	96.9
7	HCl (2 mol/L)	CuCl ₂ (0.1 eq.)	O ₂ (22 mL/min)	77.7	95.7
8	HCl (6 mol/L)	LiCl (2 eq.)	O ₂ (22 mL/min)	3.1	93.1
9	H ₂ SO ₄ (6 mol/L)	CuCl ₂ (2 eq.)	O ₂ (22 mL/min)	10.3	96.0

Conditions: microwave irradiation; solvent, H₂O for 1-2, aqueous hydrochloric acid solution for 3-8, aqueous sulfuric acid solution for 9; reaction time (60 min); reaction temperature (50 °C). Conversion and selectivity were determined by GC.



SCHEME 2: Proposed reaction mechanism of oxychlorination of phenol.

higher conversion rates, lower reaction time, and excellent selectivity, and no polychlorination products are detected. From a proposed reaction mechanism, we deduce that the reaction is inclined to form tautomeric radicals **C** that can be rapidly captured by chlorine atoms and convert into *para*-substituted products.

Competing Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Acknowledgments

This work is supported by the Project of Shandong Province Science and Technology Development Plan (Grant no. 2014GGX102023).

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