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HIGHLY EFFICIENT, PARA-SELECTIVE OXYCHLORINATION OF AROMATIC COMPOUNDS USING POTASSIUM CHLORIDE AND OXONE®*

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ABSTRACT

A highly efficient, regioselective method for oxychlorination of aromatic compounds is possible through electrophilic substitution of chlorine generated *in situ* from KCl as a chlorine source and Oxone® as an oxidant for the first time.

Chlorinated aromatic compounds have a wide diversity of uses. They can serve as precursors for numerous functionalities, such as phenols aromatic ethers and thioethers, amines, arylhydrazines, benzonitriles, fluoroaromatic, silylated aromatics and aromatic hydrocarbons.[1] The chlorination of aromatic compounds has been extensively described using many reagents,[2] such as molecular chlorine,[3] sulfuryl chloride,[4] alkyl and acyl

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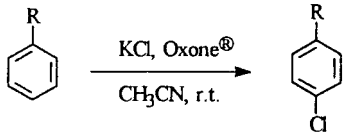
hypochlorites,[5] inorganic chlorides,[6] KCl/*m*-CPBA/18-crown-6,[7] KCl/$NaBO_3$/Na_2WO_4,[8] KCl/H_2O_2/NH_4VO_3,[9] N-chloro-succinimide,[10] benzyltrimethyl ammonium tetrachloroiodate ($BTMAICl_4$),[11] dichlorinemonoxide (Cl_2O),[12] $PhICl_2$ in trifluoroacetic acid[13] and *N*-chloroamines,[14] -amides and -sulfonamides.[15] The methods reported have some limitations such as use of strong and non-selective chlorinating agents, toxic and expensive reagents, low yields and long reaction times.

Industrial synthesis of chloroarenes are commonly performed with molecular chlorine in the presence of Lewis or mineral acids at 20–80°C.[16] Catalysts such as aluminium(III), iron(III), tin(IV) or zinc(II) chlorides, to name just a few, have been used widely.[17] The major disadvantages are poor regioselectivities, corrosion caused by the highly reactive species and hydrogen chloride side product and disposal problems. Thus, a great deal of efforts are being directed toward carrying out the chlorination of arenes in the gas and liquid phases using alumino-silicate catalysts, especially zeolites, in order to achieve better selectivities under milder conditions.[18] Irreversible damage caused to the zeolites by hydrogen chloride is, however, a stumbling block, so that industrial applications are still rare. To overcome these difficulties some researchers have utilized a combination of hydrochloric acid and suitable oxidant[19] such as *tert*-butyl hydroperoxide, hydrogen peroxide or *m*-chloroperbenzoic acid, which in situ generates positive chlorine species for the chlorination of aromatic substrates.

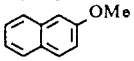
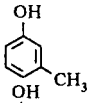
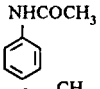
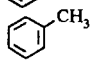
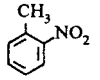
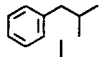
In this communication we report a new method for the para selective (regioselective) oxychlorination of aromatic compounds using commercially available Oxone® as an oxidant and KCl as a chlorine source. We observed smooth chlorinations in acetonitrile without any additional catalyst.



Scheme 1.

A number of different aromatic substrates were subjected to the chlorination reaction to test the generality of this method and the results are summarized in Table 1. These reactions proceeded efficiently under mild conditions in acetonitrile with high yields and regioselectivity with KCl and Oxone®. Potassium peroxymonosulfate is an inexpensive and readily accessible oxidizing agent. It is commonly used as

Table 1. Regioselective Oxychlorination of Aromatic Compounds with KCl and Oxone® in Acetonitrile[a]

Entry	Substrate	Time (h)	Conversion (%)	Yield (%)[b]		
				Para	Ortho	Di
1.		15	98	90	8	–
2.		15	90	72	15	3
3.		15	99	5	94	–
4.		15	99	69	22	8
5.		15	82	77	5	–
6.		15	86	73	13	–
7.		48	63	39	6	18
8.		15	90	82	8	–
9.		24	98	69	29	–
10.		24	<5	<5	–	–
11.		24	86	66	17	3
12.		24	75	72	2	1
13.		24	77	66	11	–
14.		24	–	–	–	–
15.		24	–	–	–	–
16.		24	–	–	–	–

a : Substrate (2 mmol), KCl (2.2 mmol), Oxone® (2.2 mmol), CH_3CN (10 ml), r.t.

b : The products were characterized by NMR, Mass, GC analysis.

Oxone® ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$) and is a versatile oxidant for the transformation of a wide range of functional groups.[20] The results shown in Table 1 indicate that the reaction is successful for a variety of aromatic compounds.

Introduction of an electron-withdrawing group on the aromatic ring substantially decreases the rate of ring chlorination (Table 1, Entries 7 and 10) while on electron donating group increases it. As is evident from the Table 1 aromatic substrates of greater, moderate reactivity ex. methoxy, hydroxy and alkyl benzenes react readily with KCl/Oxone® to give essentially quantitative yields of the monochloro derivatives with high para selectivity with little or no tendency to polychlorination. Less reactive substrates such as nitrobenzene, chlorobenzene, benzoic acid could not be chlorinated even at elevated temperature (80°C). In the case of 2-nitrophenol the corresponding monochloro phenol (4-chloro-2-nitrophenol) was obtained in moderate yields.

The results show that chlorination of toluene (Table 2, Entry 4) with two fold excess of KCl and Oxone® afforded (mono) 2 and 4-chlorotoluene in 97% yield and a small amount (3%) of 2,4-dichlorotoluene, whereas anisole, phenol and acetanilide (Table 2, Entries 1–3) furnished dichlorinated compounds as a major products along with a small amount of monochlorinated compounds. The interesting difference between highly activated aromatics gives the dichlorinated compounds whereas moderately activated aromatics gives the monochlorinated compounds. Then, we can selectively prepare the desired chloro-substituted compound by using calculated amount of KCl and Oxone® in case of highly activated aromatics. A wide range of solvents has been employed in these reactions (Table 3), including carbon tetrachloride, hexane, dichloromethane, methanol and acetonitrile. However, the yields, rates of reaction and degree of para-selectivity generally appeared to be optimum in acetonitrile.

Table 2. Oxychlorination of Aromatic Compounds with 2.2 Equiv. of KCl and Oxone® in Acetonitrile[a]

Substrate	Time (h)	Conversion (%)	Yield (%)[b]			
			Para	*Ortho*	Di	Others
1. Anisole	15	100	12	–	81	7
2. Phenol	15	100	20	2	78	–
3. Acetanilide	15	100	–	12	61	27
4. Toluene	24	100	68	29	3	–

[a]Substrate (2 mmol), KCl (4.4 mmol), Oxone® (4.4 mmol), CH_3CN (10 ml), r.t.
[b]The products were characterised by NMR, Mass, GC analysis.

Table 3. The Effect of Solvent on the Oxychlorination of Anisole Using KCl-Oxone® System[a]

Solvent	Time (h)	Conversion (%)	Yield (%)[b]		
			Para	*Ortho*	Di
1. Acetonitrile	15	98	90	8	–
2. Methanol	15	97	72	24	1
3. Dichloromethane	15	5	5	–	–
4. Carbon tetrachloride	15	–	–	–	–
5. Hexane	15	–	–	–	–

[a]Anisole (2 mmol), KCl (2.2 mmol), Oxone® (2.2 mmol), Solvent (10 ml), r.t.
[b]The products were characterised by NMR, Mass, GC analysis.

Two experimental parameters deserve emphasis. First, the nature of the solvent has a dramatic influence on the regioselectivity. Switching from the non-polar carbon tetrachloride (polarity = 0.0D) to the strongly polar acetonitrile (polarity = 3.92D) results in a change of yields from 0 to 98% for anisole chlorination. Even greater paraselectivity (*para*/*ortho* upto 90/8) was obtained by using acetonitrile as a solvent compared to methanol. Secondly, the nature of oxidant used has a dramatic influence on the yields and selectivity. We surveyed the oxychlorination with various oxidants. Reactions were conducted with anisole as a probe-substrate at room temperature in acetonitrile. However, Oxone® is far superior to the other oxidants for example, H_2O_2 give little of the product and TBHP and molecular O_2 showed no sign of reaction after 15 h. The best oxidant is Oxone® from the standpoint of highest yield and selectivity.

The reaction proceeds efficiently in high yields at ambient temperature and pressure. The role of Oxone® was confirmed by conducting a blank experiment, where the formation of chloro compound was not observed.

$$\mathrm{ArH + KCl + 2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4} \rightarrow \mathrm{ArCl + KOH + K_2S_2O_8 \cdot KHSO_4 \cdot K_2SO_4 + H_2O} \quad (1)$$

$$\mathrm{2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4 + KCl} \rightarrow \mathrm{KOH + HOCl + K_2S_2O_8 \cdot KHSO_4 \cdot K_2SO_4} \quad (2)$$

$$\mathrm{2HOOSO_3K \rightarrow 2HO^{\cdot} + 2^{\cdot}OSO_3K} \quad (3)$$

$$\mathrm{KCl + 2HO^{\cdot} + 2^{\cdot}OSO_3K \rightarrow KOH + HOCl + K_2S_2O_8} \quad (4)$$

$$\mathrm{ArH + HOCl \rightarrow ArCl + H_2O} \quad (5)$$

A typical oxychlorination of an aromatic compound in the presence of Oxone® proceeds according to the stoichiometry of Equation 1. It is believed that the chlorination proceeds via the formation of hypochlorous acid. The hypochlorous acid has higher instability due to pronounced ionic nature and thus more reactivity towards the aromatic nucleus. The absence of chlorination of the ring methyl group (Table 1, Entries 9–13) is indicative of the electrophilic mechanism of the reaction rather than a radical pathway. Furthermore, chlorination of alkylbenzenes gives large amounts of benzyl chlorides as side products,[21] such drawbacks could be avoided using this system.

In conclusion, we have developed a novel system for the regioselective oxychlorination of aromatic compounds by using KCl and Oxone® in acetonitrile under ambient conditions. The results reported here demonstrate that reagent system possess considerable practical advantages over traditional reagents for electrophilic chlorination reactions. The commercial availability of the reagents and reactions are clean, high yielding and work-up is simple. The absence of side chain chlorination products in reaction conducted in acetonitrile suggests a substantial increase in the rate of the ionic process. We are currently extending this methodology to other halogenation reactions.

General Procedure for the Chlorination of Aromatic Compounds: Oxone® (2.2 mmol) was added to a well stirred solution of KCl (2.2 mmol) and substrate (2 mmol) in acetonitrile (10 ml) and the reaction mixture was allowed to stir at room temperature. The reaction was monitered by thin layer chromatography (TLC). After the completion of the reaction, the mixture was filtered and solvent evaporated under reduced pressure. The products were purified by column chromatography over silica gel and confirmed by ^{1}H NMR and Mass spectra.

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