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Efficient Oxidative Chlorination of Aromatics on Saturated Sodium Chloride Solution

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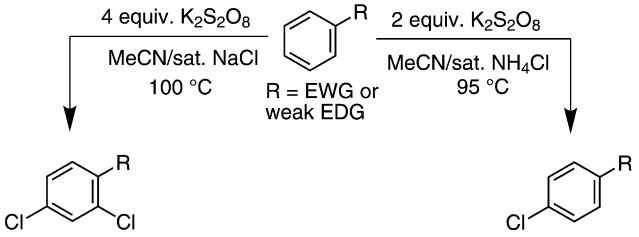
Abstract: An efficient metal-free system using saturated aqueous sodium chloride/aqueous ammonium chloride solution as chlorine source and potassium persulfate as a cheap oxidant for the chlorination of various aromatic compounds including deactivated ones has been developed that proceeds without any acid additive in an excellent regioselective manner. The easy-to-handle aqueous solution/acetonitrile biphasic system as solvent and no need for precautionary measures make this process very practical.

Keywords: aromatic compounds; biphasic conditions; chlorination; metal-free reaction; potassium persulfate

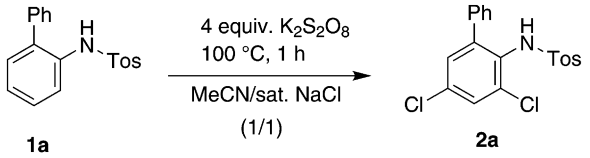
Chlorinated aromatic compounds are very valuable building blocks in pharmaceutical synthesis, when considering the indispensable role of halogenated compounds in transition metal-mediated coupling reactions.[1,2] Traditionally, molecular chlorine was commonly used with a metal catalyst for electrophilic arene chlorination under relatively harsh conditions.[3] Significant progress was achieved by using alternative oxidized halogen reagents (*N*-chlorosuccinimide, NCS), which is less toxic and easier to handle.[4] Olah and co-workers reported the acid-promoted NCS chlorination of aromatic compoundss with an excess amount of BF_3-H_2O under heating conditions;[4] Recently, the direct oxidative chlorination with chloride anions (sources such as HCl, KCl etc.) in the presence of an oxidant has received more attention from the green chemistry perspective.[5,6] To achieve excellent regioselectivity, a selected metal catalyst is usually a must in oxidative chlorination due to the high reactivity of those chlorinating reagents.[7] However, to the best of our knowledge, in most of the cases, chlorination of deactivated aromatic compounds suffers from very low yield or even no reaction. Herein, we report a metal-free oxidative chlorination on saturated NaCl/NH_4Cl aqueous solution with the cheap oxidant potassium persulfate, which works well for various aromatic compounds including deactivated ones. In this work, both dichloro products and monochloro products could be achieved in regioselective manners by simply changing the reaction conditions. Generally, chlorination reactions were more reactive in the biphasic system of MeCN/saturated NaCl (producing dichloro derivatives in most cases) than those reactions in the system of MeCN/saturated NH_4Cl aqueous solution (producing mono chloro derivatives in most cases) (Scheme 1).



Scheme 1. Efficient combined systems for the chlorination of aromatic compounds.

Peroxydisulfate has been extensively studied as an oxidant in Elbs and Boyland–Sims oxidations to introduce hydroxy groups into aromatic rings without cleavage of aromatic side chains,[8] it has not been widely used in oxidative chlorination, probably due to the poor selectivity and narrow substrate scope showed in the initial study.[9,10] Moreover, Ledwith et al. found that with $Na_2S_2O_8$ and LiCl it was possible to achieve chlorinated hydrocarbons on the aromatic ring rather than on the side chain in the presence of $CuCl_2$ and HCl.[10] However, the scope investigation showed that only substrates more reactive (electron-rich) than benzene could give significant amounts of

Table 1. Optimization of the reaction conditions.[a]



1a 2a

Entry	Solvent	Oxidant (4 equiv.)	Yield[b]
1[c]	MeCN	$K_2S_2O_8$	N.R.
2[c]	MeCN/water (v/v = 1/1)	$K_2S_2O_8$	complex
3	MeCN/sat. NaCl (v/v = 1/1)	$K_2S_2O_8$	92%
4[d]	MeCN/sat. NaCl (v/v = 1/1)	$K_2S_2O_8$	78%
5	MeCN/sat. NaCl (v/v = 1/1)	$PhI(OAc)_2$	0

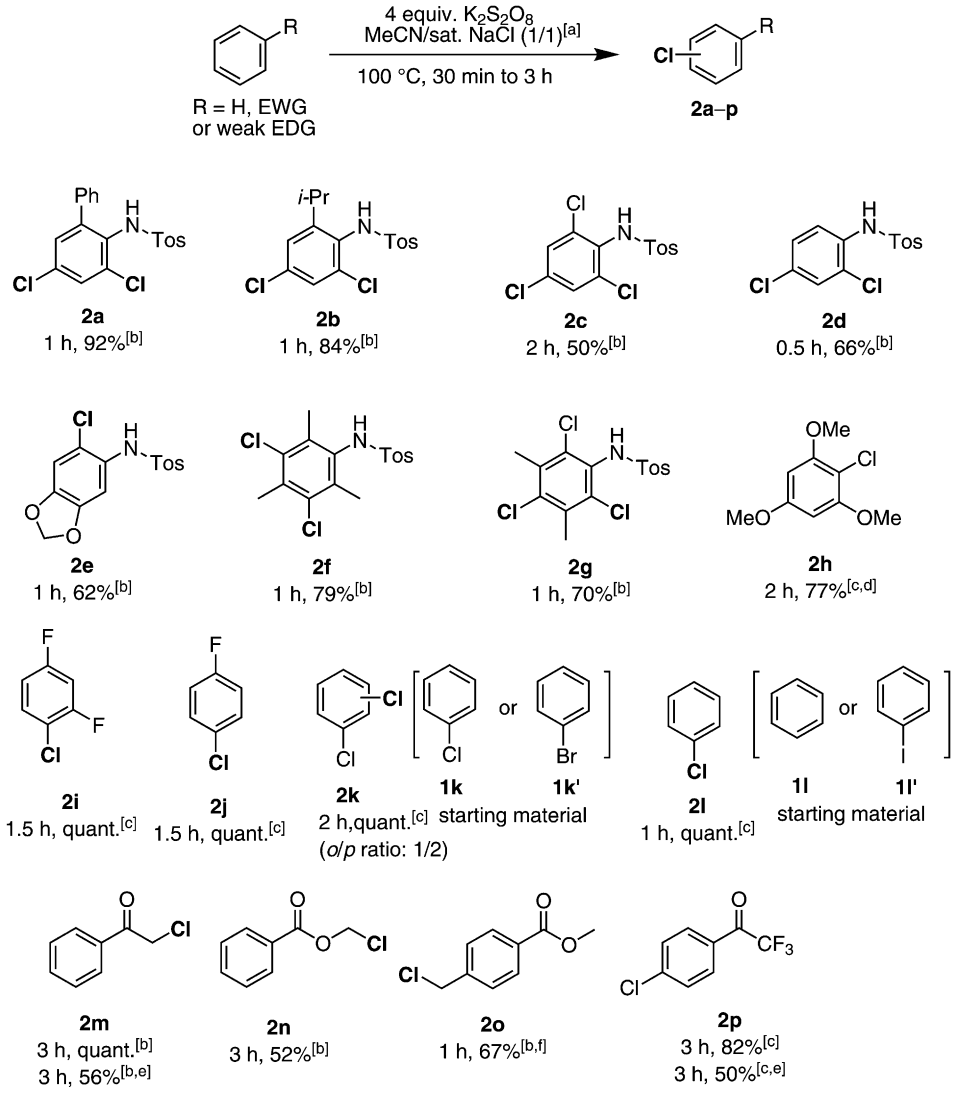
[a] The reaction was carried out at 100 °C for 1 h in a sealed vial with a combined solvent (1 mL) of MeCN/sat. NaCl (v/v = 1/1) using **1** (0.25 mmol) and $K_2S_2O_8$ (1 mmol) as an oxidant.
[b] Isolated yield.
[c] 4 equiv. NaCl were used as chlorine source.
[d] 3 equiv. $K_2S_2O_8$ were used.

chlorinated products and the isomer distribution was similar to that of conventional electrophilic substitution.[10] In our exploration of oxidative coupling reactions, we found that potassium persulfate was a much more effective oxidant in the chlorination of aromatic compoundss so that the reaction could occur even in the absence of any acid additive under the combined system of acetonitrile and saturated NaCl solution. Encouraged by this finding, various conditions were optimized in the chlorination of sulfonamide **1a** and we found that with 4 equiv. $K_2S_2O_8$ the reaction could afford the dichloro product in 92% yield in MeCN/saturated NaCl (v/v = 1/1, for details see Table S1 in the Supporting Information).[11] In the control experiment without any water additive, the reaction did not occur, which indicated the important role of water in this conversion (Table 1, entry 1). Increasing the water ratio in the mixed solvent system led to strong side reactions (entry 2). Saturated NaCl solution seems to be the perfect reaction medium in order to provide the water and chlorine source needed for chlorination (entry 3).[12] The use of $PhI(OAc)_2$ led to formation of carbazole (entry 5). And an excess amount of oxidant (4 equiv.) was necessary for high yield (entry 2). MeCN proved to be the best co-solvent in screening of other solvents including EtOAc, EtOH and methyl lactate.

Having thus found an efficient system for the chlorination of aromatic compounds, we next investigated its scope (Scheme 2). Upon replacement of phenyl with various other functional groups including isopropyl, hydrogen on the aromatic ring, the chlorination reactions all gave dichloro products in different reaction times (**2a**–**d**). With a 1,3-dioxole group to block the *para* position, the *ortho*-monochloro product instead of the dichloro one was obtained (**2e**). When R is electron-rich trimethyl or dimethyl groups, dichloro (**2f**) and trichloro (**2g**) products were achieved, respectively. Simple electron-rich arenes such as 1,3,5-trimethoxybenzene could be chlorinated with only 1.1 equiv. $K_2S_2O_8$ producing the monochloro arene (**2h**). However, chlorination of mesitylene and phenol gave messy products even in the presence of 1.1 equiv. $K_2S_2O_8$, which suggested that the sulfonamide group on the aromatic ring is beneficial for the high selectivity and the chlorination might proceed *via* an *N*-chloro salt intermediate.[13]

To our delight, deactivated aromatic compounds which were extremely difficult or even inert for chlorination in systems of MeCN/HCl/$Na_2S_2O_8$/LiCl/$CuCl_2$[9] or other oxidants/Cl^-[5,14] were also suitable substrates for the system of MeCN/saturated NaCl/$K_2S_2O_8$. Chlorinations of 1,3-difluorobenzene and fluorobenzene were completed in 1.5 h producing *para*-chloro products quantitatively. And product **2i** could be a precursor for the synthesis of Diflunisal (Dolobid, Merck & Co.), which is a non-opioid, non-steroidal anti-inflammatory drug.[15] Also, chlorination of benzene could be completed in 1 h, producing chlorobenzene almost quantitatively. Interestingly, for chlorobenzene and bromobenzene, chlorination reactions gave the same product, namely dichlorobenzene with almost same 2/1 *p*/*o* ratio). And chlorination of iodobenzene gave an almost quantitative yield of chlorobenzene product in 1 h. It was known that in the HCl/H_2O_2 system, aryl iodide would be oxidized to aryliodine(III) dichloride.[6] However, in our system, no similar intermediates were detected and we believe the product of chlorodeiodination is formed directly from the parent iodoarene. These results also indicate that the chlorination of bromobenzene may proceed *via* a radical halogen exchange and subsequent chlorination of a chlorobenzene intermediate. For acetophenone, chlorination occurred on side chain instead of the aromatic ring (**2m**). Electron-deficient 2,2,2-trifluoroacetophenone is also a suitable substrate yielding the *p*-chlorinated product (**2p**). Meanwhile, chlorination of methyl benzoate gave the chloromethyl ester (**2n**),[16] and chloromethyl esters are recognized as valuable intermediates for the preparation of prodrugs.[17]

In order to compare the reactivity of the methyl groups on the aromatic ring and ester part, methyl 4-methylbenzoate was also examined in the presence of 2 equiv. and 4 equiv. $K_2S_2O_8$, respectively. methyl 4-(chloromethyl)benzoate (**2o**) was obtained as major product in 67% yield with 2 equiv. $K_2S_2O_8$, and a mixture of methyl 4-(chloromethyl)benzoate and chloromethyl 4-(chloromethyl)benzoate was observed with 4 equiv. $K_2S_2O_8$. This result indicated that the priority order for chlorination in methyl 4-methylbenzoate is

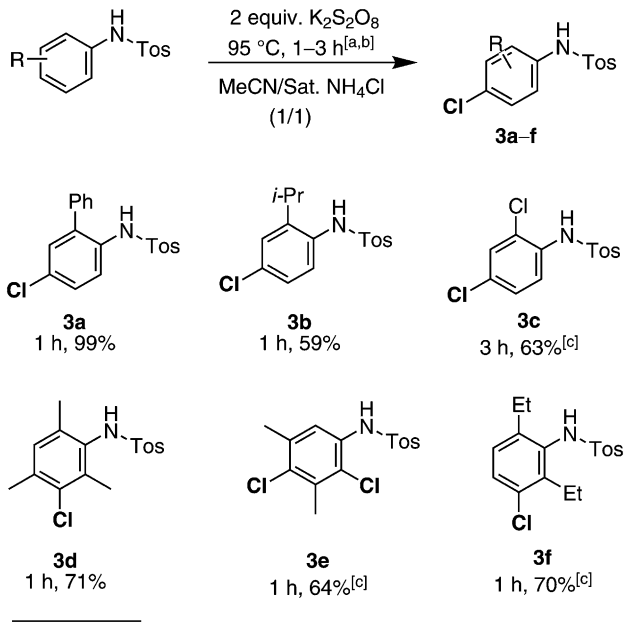


[a] The reaction was carried out at 100 °C in a sealed vial with a combined solvent (1 mL) of MeCN/sat. NaCl solution (v/v = 1/1) using aryl compound (0.25 mmol) and $K_2S_2O_8$ (1 mmol) as an oxidant.
[b] Isolated yield.
[c] Determined by ^1H NMR in CD_3CN.
[d] 1.1 equiv. $K_2S_2O_8$ was used.
[e] 1 mmol aromatic compound was used.
[f] 2 equiv. $K_2S_2O_8$ were used.

Scheme 2. Examination of various aromatic compounds in MeCN/saturated NaCl.

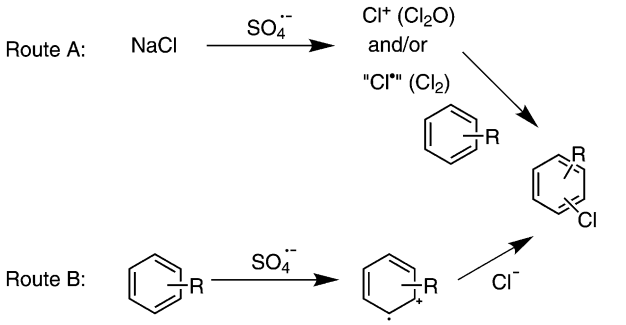
$Me_{aromatic} > Me_{ester} > H_{aromtic}$. Attempts with more electron-deficient aromatic compounds including benzonitrile, 1,2,4,5-tetrafluorobenzene and nitrobenzene in this system were not successful and reaction afforded traces of or no chlorinated product.

Further investigation proved that monochloro products could also be achieved in most cases in the presence of potassium persulfate when saturated NH_4Cl aqueous solution was used as co-solvent as well as chlorine source instead of saturated NaCl. Monochloro products at the *para*-position were usually obtained as major products regardless of an electron-donating functional group or electron-withdrawing group at the *ortho*-position of amino aromatic compounds (Scheme 3).[18] However, the *meta*-chloro product was observed in the chlorination of *o*/*p* blocked substrates with a methyl group. Chlorination of the 3,5-dimethyl amino aromatic gave the dichloro product in the presence of 4 equiv. oxidant, while chlorination of the 2,6-diethyl amino aromatic afforded only the monochloro product at the *meta* position under the same conditions. Chlorinations of fluoro-

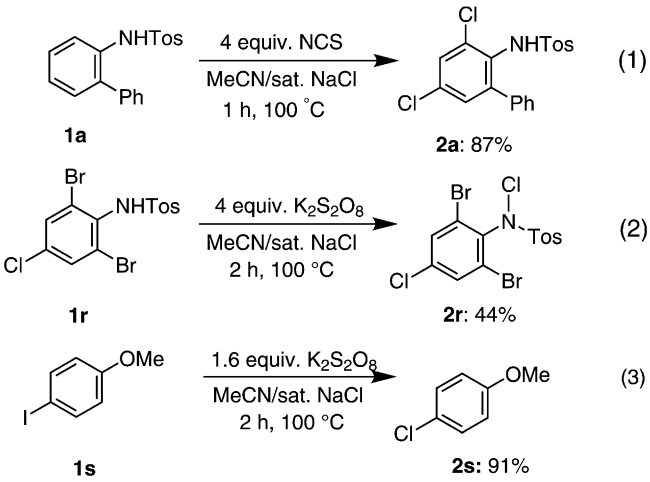


[a] The reaction was carried out at 95 °C for 1–3 h in a sealed vial with a combined solvent (1 mL) of MeCN/saturated NH_4Cl (v/v = 1/1) using aromatic compound (0.25 mmol) and $K_2S_2O_8$ (0.5 mmol) as an oxidant.
[b] Isolated yield.
[c] 4 equiv. $K_2S_2O_8$ (1 mmol) were used.

Scheme 3. Examination of various aromatic compounds in MeCN/NH_4Cl (saturated solution.



Scheme 4. Possible pathways in chlorination.



Scheme 5. Control chlorination reactions on saturated NaCl solution.

benzene, 1,3-difluorobenzene, bromobenzene and chlorobenzene gave the same products as those obtained in MeCN/saturated NaCl solution system, albeit with sharp decreases in reaction activity.

These facile and selective chlorination reactions intrigued us to explore more on how the chlorination reaction works in this biphasic system. In general, there are two possible pathways: route A: oxidation of Cl^- by $K_2S_2O_8$ ($SO_4^{\cdot-}$) into more reactive chlorinating species ["Cl^+" (Cl_2O) or "Cl_2"] which can then react with arenes *in situ*.[14] Route B: oxidation of arene by $K_2S_2O_8$ ($SO_4^{\cdot-}$) generates an aromatic cation radical, and then it reacts with Cl^- giving the chlorinated aromatics (Scheme 4). Ledwith et al. demonstrated that the route B was more probably in MeCN/HCl/$Na_2S_2O_8$/LiCl/$CuCl_2$[10] although they did not rule out the other possibility. In order to gain more insights on the mechanism in our system, a comparative chlorination reaction of sulfonamide **1a** in the presence of 4 equiv. NCS was performed and the reaction afforded the same dichloro product **2a** in similar yield as that from the reaction with $K_2S_2O_8$ [Scheme 5, Eq. (1)]. And the observance of *N*-chloro salt **2r** in the chlorination of electron-deficient arene **1r** proved the existence of "Cl^+"(Cl_2O or Cl_2) [Eq. (2)]. The relationship between the reactivity/selectivity and concentration of NaCl solution in the chlorination of 1,3-difluorobenzene was also studied in order to probe the reason for the high reactivity compared to the previous oxone/KCl system[9] (see Table S2 in the Supporting Information). In MeCN only, the combination of $K_2S_2O_8$ (4 equiv.)/NaCl (4 equiv.) was inert and 1,3-difluorobenzene was recovered, which indicated the critical role of water in the initiation of $K_2S_2O_8$. In the absence of NaCl, oxidation of 1,3-difluorobenzene occurred in minutes and an insoluble yellow solid formed under MeCN/deionized (DI) water (v/v = 1/1) at 100 °C. With a lower concentration of NaCl solution (5 wt%), the oxidation pathway of aromatic compounds was remarkably prohibited and the chlorination led to a mixture of various products and unreacted 1,3-difluorobenzene. On increasing the concentration of NaCl solution to 10 wt%, a significant amount of over-oxidized by-product (tetrachlorobenzene, see Table S2 in the Supporting Information) (11%) was observed. On further increases of the concentration of NaCl solution to 15 wt% and 20 wt%, the over-oxidized by-product dropped dramatically, and the yields of chlorinated product **2i** were increased to 95% and 98%, respectively. And in MeCN/brine system (26 wt% of NaCl solution), the by-product was sup-

pressed and only chlorinated product **2i** was observed. These results indicate that the chlorination might proceed *via* route A rather than route B in NaCl solution although the process is not fully understood yet. However, we still could not rule out route B especially in the chlorination of simple electron-rich arenes because of the higher reactivity observed in the chlorination of **1s** compared to that with iodobenzene [Eq. (3)].

In summary, we have developed metal-free systems for the chlorination of various aromatic compounds in the absence of acids in an excellent regioselective manner, even for deactivated ones. This method provides an efficient and practical way towards various chlorinated aromatic compounds which are valuable intermediates in industry due to the cheap reagents and relatively mild conditions.

Experimental Section

General Procedure for Chlorination of Aromatic Compounds

To a 10-mL headspace vial were added substrate (0.25 mmol) and MeCN (0.5 mL). Then brine (0.5 mL) and $K_2S_2O_8$ (4 equiv. or other amount) were added. After the reaction vial had been sealed with PTFE/silicone septa, it was placed in a heating block on a stirrer for 0.5 ~3 h at 100 °C. After the reaction had been completed, there were two layers in the mixture. 5 mL $Na_2S_2O_3$ solution (1 M) (or simply 5 mL deionized water) were added for quenching the reaction, followed by extraction with EtOAc (5 mL × 3). The combined organic layers were dried with anhydrous sodium sulfate. Purification of crude products after concentration with preparative TLC afforded the pure products. For halobenzene substrates, MeCN-d_3 (0.5 mL) was used instead of MeCN as solvent and the upper layer of the mixture was directly transferred to an NMR tube after simple filtration by a glass dropper filled with anhydrous sodium sulfate for measurement of the conversion yield.

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