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Highly Selective Oxidative Monochlorination To Synthesize Organic Intermediates: 2-Chlorotoluene, 2-Chloroaniline, 2-Chlorophenol, and 2-Chloro-4-methylphenol

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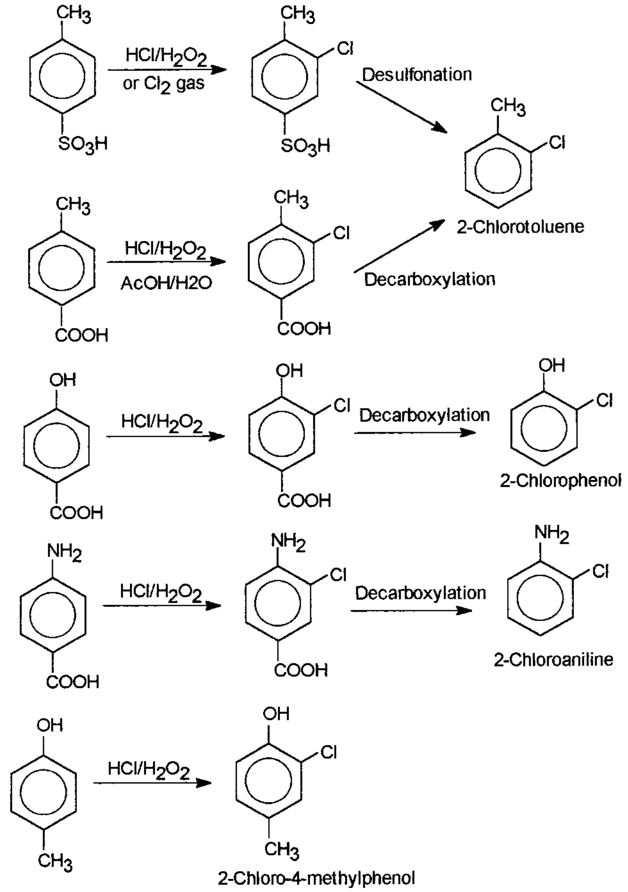
Abstract:

An alternative manufacturing process scheme was developed to synthesize monochloro-substituted aromatic compounds in high selectivity, involving oxidative chlorination by using HCl−H_2O_2. Thus, 2-chlorotoluene, 2-chloroaniline, and 2-chlorophenol were synthesized by oxidative chlorination followed by desulphonation or decarboxylation. Oxidative chlorination of 4-methylbenzenesulphonic acid, 4-methylbenzoic acid, 4-aminobenzoic acid, and 4-hydroxybenzoic acid by using a suitable ratio of reactant:HCl:H_2O_2, and their subsequent desulphonation or decarboxylation, gave 60−85% yield of the desired products. Oxidative chlorination of 4-methylphenol by using HCl−H_2O_2 gave as high as 98% selectivity to the desired 2-chloro-4-methylphenol.

Introduction

Ortho-chloro-substituted aromatic compounds have great relevance in organic process industries as intermediates for fine chemicals. In general, these are synthesized by direct chlorination of the reactant. But there is always a chance of getting an isomeric mixture[1,2] of 2- and 4-chloro-substituted products with some dichloro or trichloro compounds, from which the separation of the desired product itself is a problem. Oxidative chlorination with HCl−H_2O_2 after protection at the 4-position of the substrate and then deprotection by desulphonation or decarboxylation gives as high as 97% selectivity to the dichloro-substituted products.[3−5] H_2O_2 is added to the reaction mixture in a semibatch manner. Oxygen can also be used directly with H_2O_2 in the presence of different types of catalysts.[6−8] In this work, 4-methylbenzenesulphonic acid (MBSA), 4-methylbenzoic acid, 4-aminobenzoic acid, 4-hydroxybenzoic acid, and 4-methylphenol were chlorinated by using HCl−H_2O_2 in a less expensive solvent such as water, acetic acid, or dichloroethane. 3-Chloro-4-methylbenzenesulphonic acid (CMBSA) was desulphonated in sulphuric acid, and the other chloro-substituted benzoic acids were decarboxylated in quinoline to obtain the desired products (Scheme 1).

Scheme 1. **Oxidative chlorination, decarboxylation or desulphonation**



Experimental Section

Experimental Procedure. The oxidative chlorination experiments were carried out in a 250-mL borosilicate glass reactor equipped with a six-blade turbine impeller, four

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baffles, a dropping funnel, and a water condenser. The outgoing gases were passed through a caustic scrubber. The assembly was kept in a constant-temperature bath. A predetermined quantity of substrate and 35% hydrochloric acid were dissolved in the solvent, and the reaction mixture was kept at the desired temperature. A measured quantity of 30% hydrogen peroxide was added dropwise to the reaction mixture over a predetermined period of time, while maintaining the desired temperature within the specified range. For MBSA, the reaction mixture was directly taken for the desulphonation step without isolation. In the case of benzoic acids, after the stipulated reaction period, the reaction mixture was chilled and then filtered to remove the precipitated products. The products were then dried and taken for the decarboxylation step. In the case of 4-methylphenol, the reaction mixture was distilled to isolate the desired 2-chloro-4-methylphenol.

For desulphonation, a measured quantity of the reaction mixture after oxidative chlorination was taken into the reactor, and a calculated amount of 98% sulphuric acid was added to the reaction mixture to obtain the desired concentration of sulphuric acid in the bulk. The reaction mixture was then heated to attain the desired temperature and was kept over a specified period of time. After the stipulated reaction period, the reaction mixture was extracted with toluene. The organic layer was washed with 5% NaOH solution to remove the unreacted sulphonic acid. Then the organic layer was dried on sodium sulphate and distilled under vacuum to isolate the desired product.

A 100-mL autoclave was used for the decarboxylation reactions. Predetermined quantities of chlorosubstituted benzoic acid, solvent, and catalyst were charged in the autoclave. The autoclave was heated to the desired temperature and kept for a specified period of time. After the stipulated period of time, the reaction mixture was distilled under vacuum, using a 1-m wire mesh-packed column to isolate the desired 2-chloro compound.

Analytical Procedure. The reaction mixture after oxidative chlorination was analyzed by HPLC, under the following conditions: column, MERCK 50983, Lichrosphere 100 RP-18, 5 μm, 254 × 4 mm; mobile phase, water−acetonitrile, 3:2; flow rate, 1 mL/min; wavelength, 254 nm.

The conditions for GC used to analyze the reaction mixtures after desulphonation reaction were as follow: column, OV-17, 4 m; oven temperature, 60 °C, 5 °C/min, 120 °C, 10 °C/min, 300 °C, 5 min; injector temperature, 300 °C; detector temperature, 300 °C.

Unreacted chlorosulphonic acid was analyzed by HPLC, under the same conditions as those given for oxidative chlorination.

After decarboxylation, the reaction mixtures were analyzed by GC as well as HPLC under the same conditions as given above.

Results and Discussion

Definitions. *Conversion.* The conversion is defined as the ratio of the number of moles of the reactant reacted to the number of moles of the reactant taken.

Selectivity. The selectivity to a particular product is defined as the ratio of the number of moles of the reactant reacted for the formation of that particular product to the number of moles of reactant reacted.

Process Parameter Studies. The effects of different important process parameters on the rate of oxidative chlorination of MBSA were studied to determine the most suitable reaction conditions for maximum conversion and selectivity to monochloro products.

Mode of Reaction and Addition Time of Hydrogen Peroxide on the Rate of Oxidative Chlorination of MBSA. To determine the mode of reaction to achieve maximum conversion and selectivity, the reaction was studied in batch mode as well as semibatch mode (Table 1). It was observed that when hydrogen peroxide was added dropwise, both the conversion and the selectivity with respect to the desired product increased due to the maximum utilization and control of hydrogen peroxide concentration in the reaction mixture.

Table 1. **Oxidative chlorination of MBSA: effect of mode of reaction**[a]

mode of addition	% overall conversion	% selectivity
batch mode	47	83
semibatch mode	86	98

[a] Reaction conditions: reactant concentration, 0.87 gmol/L; hydrochloric acid, 3.48 gmol/L; hydrogen peroxide: 0.783 gmol/L; temperature, 45 °C; time, 4 h.

A 3-h addition time was preferred under these reaction conditions to achieve maximum selectivity and utilization of hydrogen peroxide (Table 2).

Table 2. **Oxidative chlorination of MBSA: effect of addition time**[a]

addition time (h)	% overall conversion	% selectivity to chloro compound
1.0	59	89
1.5	67	92
2.0	70	94
3.0	86	98

[a] Reaction conditions: reactant concentration, 0.87 gmol/L; hydrochloric acid, 3.48 gmol/L; hydrogen peroxide, 0.783 gmol/L; temperature, 45 °C.

Effect of Solvent on the Rate of Oxidative Chlorination. Different solvents such as acetic acid, aqueous hydrochloric acid, and dichloro ethane were used for these reactions. Due to the difference in the solubility of the starting materials in different solvent systems, the rate of reaction was different in each case.

In acetic acid, the rate of oxidative chlorination varied in the order 4-methylphenol > 4-hydroxybenzoic acid > 4-aminobenzoic acid > 4-methylbenzoic acid under the same reaction conditions (Table 3).

In aqueous HCl, the rate of oxidative chlorination under identical conditions followed the order 4-methylbenzenesulphonic acid > 4-aminobenzoic acid > 4-methylphenol > 4-hydroxybenzoic acid > 4-methylbenzoic acid (Table 4).

And in dichloroethane, the rate followed the order 4-methylphenol > 4-hydroxybenzoic acid > 4-aminobenzoic acid > 4-methylbenzoic acid (Table 5).

Table 3. Oxidative chlorination of benzoic acids and 4-methylphenol in acetic acid[a]

reactant	% overall conversion	% selectivity
4-methylbenzoic acid	51	98
4-aminobenzoic acid	67	98
4-hydroxybenzoic acid	74	97
4-methylphenol	82	98

[a] Reaction conditions: reactant concentration, 0.87 gmol/L; hydrochloric acid, 3.48 gmol/L; hydrogen peroxide, 0.783 gmol/L; acetic acid, 350 mL; temperature, 45 °C; reaction time, 4 h.

Table 4. Oxidative chlorination of benzoic acid and 4-methylphenol in aqueous hydrochloric acid[a]

substrate	% overall conversion	% selectivity
4-methylbenzenesulphonic acid	86	98
4-methylbenzoic acid	34	98
4-aminobenzoic acid	64	98
4-hydroxybenzoic acid	53	97
4-methylphenol	61	98

[a] Reaction conditions: reactant concentration, 0.87 gmol/L; hydrochloric acid, 3.48 gmol/L; hydrogen peroxide, 0.783 gmol/L; temperature, 45 °C; reaction time, 4 h.

Table 5. Oxidative chlorination of benzoic acids and 4-methylphenol in dichloroethane[a]

reactant	% overall conversion	% selectivity
4-methylbenzoic acid	44	98
4-aminobenzoic acid	62	98
4-hydroxybenzoic acid	64	97
4-methylphenol	76	98

[a] Reaction conditions: reactant concentration, 0.87 gmol/L of organic phase; hydrochloric acid, 3.48 gmol/L of aqueous phase; hydrogen peroxide, 0.783 gmol/L of aqueous phase; temperature, 45 °C; reaction time, 4 h.

Table 6. Effect of temperature on the oxidative chlorination of MBSA[a]

temperature (°C)	% overall conversion	% selectivity
20	7	99
30	46	98
45	86	98
60	73	81

[a] Reaction conditions: reactant concentration, 0.87 gmol/L; hydrochloric acid, 3.48 gmol/L; hydrogen peroxide, 0.783 gmol/L; reaction time, 4 h.

Table 7. Effect of mole ratio of reactant to hydrogen peroxide in the oxidative chlorination of MBSA[a]

ratio reactant:H_2O_2	% overall conversion	% selectivity to monochloro compound
1:0.5	47	99
1:0.9	86	98
1:1	86	94
1:1.5	88	62

[a] Reaction conditions: reactant concentration, 0.87 gmol/L; hydrochloric acid, 3.48 gmol/L; temperature, 45 °C; reaction time, 4 h.

Table 8. Optimum conditions and isolated yield for the oxidative chlorination of MBSA in aqueous solution[a]

overall conversion of MBSA	86%
selectivity with respect to CMBSA	98%
conversion to dichloro compound	0.4%
tarry material	0.3%
isolated yield	82%

[a] Reaction conditions: reactant concentration, 0.87 gmol/L; hydrochloric acid, 3.48 gmol/L; hydrogen peroxide, 0.783 gmol/L; reaction temperature, 45 °C; reaction time, 4h.

Table 9. Optimum conditions for the desulphonation of CMBSA to synthesize 2-chlorotoluene[a]

overall conversion of CMBSA	100%
selectivity with respect to 2-chlorotoluene	98%
tarry material	1.2%
isolated yield	95%
overall isolated yield in two steps to 2-chlorotoluene	80%

[a] Reaction conditions: concentration of CMBSA, 10% w/v; concentration of sulphuric acid, 70% w/v; reaction temperature, 220 °C; solvent, quinoline; reaction time 3 h; catalyst, cuprous oxide, catalyst loading, 1% w/v.

Effect of Temperature on the Rate of Oxidative Chlorination of MBSA. The rate of oxidative chlorination of MBSA increased markedly when the temperature was increased from 20 to 45 °C (Table 6). However, a further increase in temperature from 45 to 60 °C decreased the conversion level. This is due to the rate of decomposition of hydrogen peroxide being much faster than the rate of reaction of hydrogen peroxide with hydrochloric acid at higher temperature. In the case of 4-methylphenol, with the increase in temperature, the selectivity decreased due to the higher rate of formation of the isomeric 3-chloro-4-methylphenol. The formation of 3-chloro-4-methylphenol at 50 and 60 °C was 0.9 and 2.1%, respectively, but at 45 °C, it was only 0.3% under the given reaction conditions.

Effect of Molar Ratio of Reactant:Hydrogen Peroxide on the Rate of Oxidative Chlorination of MBSA. From the reaction stoichiometry, in order to form 1 mol of monochloro compound, 1 mol of hydrogen peroxide and 1 mol of hydrochloric acid are needed for 1 mol of reactant. In all the reactions carried out, hydrochloric acid was used at 4 mol/mol of reactant to ensure maximum utilization of hydrogen peroxide to form chlorine. The mole ratio of MBSA to hydrogen peroxide was varied from 1.0:0.5 to 1.0:1.5. It was observed that, when only 90% of the theoretical amount of hydrogen peroxide was used, 86% conversion and as high as 98% selectivity were achieved (Table 7). Thus, a ratio of 1.0:0.9 was found to be the most suitable under the reaction conditions.

Optimum Conditions. The most suitable process conditions to synthesize different products are given in Tables 8−14.

Comparison of the Rate of Oxidative Chlorination of MBSA with That of Direct Chlorination. In an effort to compare the rate of reaction of direct chlorination with that of the oxidative chlorination, MBSA was chlorinated in water by chlorine gas. It was possible to chlorinate the reactant by use of chlorine gas, but in comparison to the oxidative chlorination, the reaction rate and the selectivity to the desired

Table 10. **Optimum conditions for the oxidative chlorination of 4-aminobenzoic acid**[a]

overall conversion of 4-aminobenzoic acid	67%
selectivity with respect to monochloro compound	98%
conversion to dichloro compound	0.3%
tarry material	0.5%
isolated yield	63%

[a] Reaction conditions: reactant concentration, 0.87 gmol/L; hydrochloric acid, 3.48 gmol/L; hydrogen peroxide, 0.783 gmol/L; reaction temperature, 45 °C; acetic acid, 350 mL; reaction time, 4 h.

Table 11. **Optimum conditions for the decarboxylation of 3-chloro-4-aminobenzoic acid to synthesize 2-chloroaniline**[a]

overall conversion of 3-chloro-4-aminobenzoic acid	100%
selectivity with respect to 2-chloroaniline	98%
tarry material	1.1%
isolated yield	96%
overall isolated yield of 2-chloroaniline in two steps	60

[a] Reaction conditions: reactant concentration, 10% w/v; temperature, 220 °C; catalyst, cuprous oxide; catalyst loading, 1% w/v; solvent, quinoline; reaction time, 6 h.

Table 12. **Optimum conditions for the oxidative chlorination of 4-hydroxybenzoic acid**[a]

overall conversion of 4-hydroxybenzoic acid	74%
selectivity with respect to monochloro compound	97%
conversion to dichloro compound	0.7%
tarry material	0.9%
isolated yield	69%

[a] Reaction conditions: reactant concentration, 0.87 gmol/L; hydrochloric acid, 3.48 gmol/L; hydrogen peroxide, 0.783 gmol/L; reaction temperature, 45 °C; acetic acid, 350 mL; reaction time, 4 h.

Table 13. **Optimum conditions for the decarboxylation of 3-chloro-4-hydroxybenzoic acid to synthesize 2-chlorophenol**[a]

overall conversion of 3-chloro-4-hydroxybenzoic acid	97%
selectivity with respect to 2-chlorophenol	98%
tarry material	1.3%
isolated yield	92%
overall isolated yield of 2-chlorophenol in two steps	63%

[a] Reaction conditions: reactant concentration, 10% w/v; temperature, 220 °C; catalyst, cuprous oxide; catalyst loading, 1% w/v; solvent, quinoline; reaction time, 6 h.

Table 14. **Optimum conditions for the oxidative chlorination of 4-methylphenol to synthesize 2-chloro-4-methylphenol**[a]

overall conversion of 4-methylphenol	82%
selectivity with respect to 2-chloro-4-methylphenol	98%
conversion to 3-chloro-4-methylphenol	0.3%
conversion to dichloro compound	0.25%
tarry material	1.1%
isolated yield	78%

[a] Reaction conditions: reactant concentration, 0.87 gmol/L; hydrochloric acid, 3.48 gmol/L; hydrogen peroxide, 0.783 gmol/L; reaction temperature, 45 °C; acetic acid, 350 mL; reaction time, 4 h.

Table 15. **Comparison of the rate of oxidative chlorination of MBSA with that of direct chlorination**[a]

chlorination	% conversion	% selectivity
oxidative chlorination with HCl−H_2O_2	86	98
direct chlorination with Cl_2 gas	43	83

[a] Reaction conditions: reactant concentration, 0.87 gmol/L; temperature, 45 °C; reaction time, 4 h.

monochloro products were low under otherwise the same reaction conditions (Table 15).

Comparison of the Efficiency of the New Processes with That of the Existing Processes. 2-Chlorotoluene can be prepared by chlorination of toluene or by diazotization of 2-toluidine. In the case of direct chlorination, there is always a chance of gettting an isomeric mixture of 2- and 4-chlorotoluene, from which the separation of the 2-chloro compound is very difficult. In the case of toluidine,[8] a low yield of diazonium salt complicated the process scheme. Direct chlorination of phenols is carried out at a temperature of 50−150 °C. This process has two main disadvantages: (i) Here, the chlorine ratios must be controlled to avoid the formation of di- and trisubstituted products. (ii) Formation of 4-chlorophenol is practically unavoidable. Direct chlorination or bromination of cresols always ends up with byproducts and tarry material, which results in a very low selectivity. In this process scheme, 2-chlorotoluene has been prepared by oxidative chlorination of MBSA followed by desulphonation. It is convenient to start with an easily available and less expensive raw material than to start with a costly raw material like 4-toluidine. As the selectivity towards the desired product obtained in this process scheme was very high, the separation was easier than in the existing processes. There is no need to use costly solvents for selective chlorination. A less expensive solvent like water, acetic acid, or dichloroethane was used in this investigation. Homogeneity of the reaction mixture was an added advantage for this process scheme, for which the rate of reaction was higher than those of the processes described in the literature. The isolated yields of 2-chlorotoluene, 2-chloroaniline, 2-chlorophenol, and 2-chloro-4-methylphenol were also very high.

Conclusions

It has been shown that some important monochloro-substituted organic intermediates can be prepared selectively by this method. Though direct chlorination using chlorine gas is an industrial process, oxidative chlorination may also be used as a process scheme to manufacture high-priced, low-volume monochloro-substituted aromatic intermediates in very high selectivity.

In the oxidative chlorination, the selectivity towards the monochloro compounds was very high. Only 0.4% of dichloro compound and 0.3% of tarry material were formed as the byproduct under the best suitable reaction conditions.

Desulphonation of CMBSA was successfully performed to give 2-chlorotoluene in high yield.

Decarboxylation of 3-chloro-4-methylbenzoic acid, 3-chloro-4-aminobenzoic acid, and 3-chloro-4-hydroxybenzoic acid was successfully performed to give 2-chlorotoluene, 2-chloroaniline, and 2-chlorophenol in very high yield.

Oxidative chlorination of 4-methylphenol gave almost 99% selectivity to the monochloro compound.

For oxidative chlorination and desulphonation reactions, glass-lined or titanium-lined reactors are needed.

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