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Oxidative Chlorination, Desulphonation, or Decarboxylation To Synthesize Pharmaceutical Intermediates: 2,6-Dichlorotoluene, 2,6-Dichloroaniline, and 2,6-Dichlorophenol

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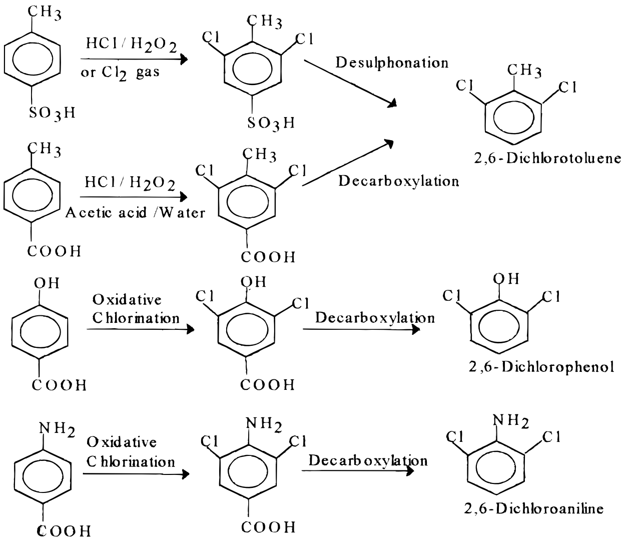
Abstract:

An alternative manufacturing process scheme was developed for 2,6-dichlorotoluene, 2,6-dichloroaniline, and 2,6-dichlorophenol, involving oxidative chlorination after protection of the starting material in the para position followed by deprotection involving desulphonation or decarboxylation. Oxidative chlorination of 4-methylbenzenesulphonic acid, 4-methylbenzoic acid, 4-aminobenzoic acid, and 4-hydroxybenzoic acid by using HCl−H_2O_2, and their subsequent desulphonation or decarboxylation, gave a 60−75% yield of the desired product.

Introduction

2,6-Dichloro-substituted compounds have great relevance in process industries as intermediates for fine chemicals and pharmaceuticals. In general, these are synthesized by direct chlorination of the reactant. But there is always a chance of getting a mixture of chloro-substituted products, from which the separation of the desired product itself is a problem. Chlorine gas is usually used for chlorination. HCl−H_2O_2 can also be used by adding hydrogen peroxide in a semibatch manner.[1] Trifluoroacetic acid[2] is used as the solvent. Oxygen can also be used directly with H_2O_2 in the presence of different types of catalysts.[3−5] In this work, 4-methylbenzenesulphonic acid, 4-methylbenzoic acid, 4-aminobenzoic acid, and 4-hydroxybenzoic acid were chlorinated by using HCl−H_2O_2 in a less expensive solvent such as water or acetic acid. 3,5-Dichloro-4-methylbenzenesulphonic acid (DCMBSA) was desulphonated in sulphuric acid. Hydrochloric acid[6] or phosphoric acid[7] can also be used. Decarboxylation of aromatic acids can be done under various conditions.[8−12] In this work, dichloro-substituted aromatic acids were decarboxylated to obtain the desired products (Scheme 1).

Scheme 1. **Oxidative chlorination, decarboxylation, or desulphonation to synthesize pharmaceutical intermediates**



Experimental Section

Oxidative Chlorination. The experiments were carried out in a 250-mL borosilicate glass reactor equipped with a six-blade turbine impeller, four 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, maintaining the desired temperature within the specified range. For 4-methylbenzenesulphonic acid, 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 cooled and then filtered to remove the precipitated products. The products were then dried and taken for the decarboxylation step.

The reaction mixture was analyzed by HPLC. Column used: MERK 50983, Lichrosphere 100 RP-18, 5 μm, 254

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min × 4 mm. Conditions: mobile phase, water−acetonitrile (3:2); flow rate, 1 mL/min; wavelength, 254 nm.

Desulphonation. The experiments were carried out in a 250-mL borosilicate glass reactor equipped with a six-blade turbine impeller and a condenser. The assembly was kept in a constant-temperature oil bath. A measured quantity of the reaction mixture after oxidative chlorination was taken into the reactor. 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. Two-milliliter samples were withdrawn at regular intervals, extracted with a measured quantity of benzene or toluene, and analyzed by gas chromatography. After the stipulated reaction period, the reaction mixture was extracted with benzene. The benzene 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.

The conditions for GC are 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 dichlorosulphonic acid was analyzed by HPLC; conditions are the same as those given in Oxidative Chlorination.

Decarboxylation. A 100-mL autoclave was used for the decarboxylation reactions. Predetermined quantities of chloro-substituted acids, solvent, and catalyst were charged in the autoclave. The autoclave was heated to the desired temperature and kept for a specified period of time. Samples (1−2 mL) were withdrawn after regular intervals of time and were analyzed by GC as well as HPLC. After the stipulated period of time, the reaction mixture was worked up in different manners, depending upon the solvent used.

Solvent: Quinoline. After the specified period of time, the reaction mixture was distilled under vacuum using a 1-m wire mesh packed column to isolate the dichloro compound.

Solvent: N,N-Dimethylaniline. The reaction mixture was washed with 5% NaOH solution to remove the unreacted benzoic acids. Then the organic layer was distilled under vacuum using a 1-m column to isolate the desired products.

Solvent: Water. The reaction mixture was extracted with benzene or toluene. The organic layer was washed with 5% NaOH solution to remove the unreacted benzoic acids. The organic layer was then distilled under vacuum using a 1-m column to isolate the desired products.

Results and Discussion

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

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

Oxidative Chlorination. *Batch Mode vs Semi-Batch Mode.* To determine conditions for maximum conversion, the reaction was studied in batch mode as well as semi-batch mode. It was observed that, when hydrogen peroxide was added dropwise, the conversion of 4-methylbenzenesulphonic acid was 78% compared to 52% when the reaction was done in a batch mode (Table 1).

Table 1. **Chlorination of 4-methylbenzenesulphonic acid: effect of mode of reaction**[a]

mode of addition	overall conversion (%)	selectivity (%)
batch	52	92.9
semi-batch	82	96.0

[a] Reaction conditions: reactant concentration, 0.87 gmol/L; hydrochloric acid, 4.38 gmol/L; hydrogen peroxide, 1.914 gmol/L; temperature, 60 °C; time, 4 h.

Table 2. **Chlorination of 4-methylbenzenesulphonic acid: effect of addition time**[a]

addition time (h)	overall conversion (%)	selectivity for dichloro compound (%)
1.0	65	92
1.5	72	94
2.0	78	96

[a] Reaction conditions: Reactant concentration, 0.87 gmol/L; hydrochloric acid, 4.38 gmol/L; hydrogen peroxide, 1.914 gmol/L; temperature, 60 °C; reaction time including addition time, 4 h.

Table 3. **Oxidative chlorination of benzoic acids in acetic acid**[a]

reactant	overall conversion (%)	selectivity (%)
4-methylbenzoic acid	50	94
4-aminobenzoic acid	68	93
4-hydroxybenzoic acid	76	96

[a] Reaction conditions: reactant concentration, 0.87 gmol/L; hydrochloric acid, 4.38 gmol/L; hydrogen peroxide, 1.914 gmol/L; temperature, 60 °C; solvent, acetic acid; acetic acid, 350 mL; reaction time, 4 h.

With an increase in addition time, the overall conversion of 4-methylbenzenesulphonic acid was increased (Table 2). Thus, to get maximum utilization of hydrogen peroxide, a 2-h addition time is preferred under these reaction conditions.

Effect of Solvent on Rate of Oxiadative Chlorination. In the cases of 4-methylbenzoic acid, 4-aminobenzoic acid, and 4-hydroxybenzoic acid, acetic acid was used as solvent for the oxidative chlorination. The conversion varied from substrate to substrate: 76% conversion was obtained for 4-hydroxybenzoic acid, 68% for 4-aminobenzoic acid, but only 50% for 4-methylbenzoic acid (Table 3) under the same reaction conditions.

With aqueous HCl as the solvent, it was observed that the rate of reaction was higher for 4-methylbenzenesulphonic acid and the rate was very poor for 4-methylbenzoic acid (Table 4). This was because the order of the solubility of the reactants in hydrochloric acid−water solvent system was in the following order: 4-methylbenzenesulphonic acid > 4-aminobenzoic acid > 4-hydroxybenzoic acid > 4-methylbenzoic acid.

Effect of Temperature on Rate of Oxiadative Chlorination. The chlorination of 4-methylbenzenesulphonic acid was

Table 4. **Oxidative chlorination of benzoic acids in aqueous hydrochloric acid**[a]

substrate	overall conversion (%)	selectivity (%)
4-methylbenzoic acid	36	82
4-aminobenzoic acid	67	94
4-hydroxybenzoic acid	52	89

[a] Reaction conditions: reactant concentration, 0.87 gmol/L; hydrochloric acid, 4.38 gmol/L; hydrogen peroxide, 1.914 gmol/L; temperature, 60 °C; reaction time, 4 h.

Table 5. **Effect of temperature on the oxidative chlorination of 4-methylbenzenesulphonic acid**[a]

temp (°C)	overall conversion (%)	selectivity (%)
30	15	91
40	46	87
50	65	88
60	82	96
70	79	96
80	54	97

[a] Reaction conditions: reactant concentration, 0.87 gmol/L; hydrochloric acid, 4.38 gmol/L; hydrogen peroxide, 1.914 gmol/L; reaction time, 4 h.

Table 6. **Effect of mole ratio of reactant to hydrogen peroxide in the oxidative chlorination of 4-methylbenzenesulphonic acid**[a]

reactant:H_2O_2	overall conversion (%)	selectivity for dichloro compound (%)
1:1	68	8
1:2	75	89.3
1:2.1	78	95.87
1:2.2	82	96.3
1:2.5	84	96

[a] Reaction conditions: reactant concentration, 0.87 gmol/L; hydrochloric acid, 4.38 gmol/L; hydrogen peroxide, 1.914 gmol/L; temperature, 60 °C; reaction time, 4 h.

studied by using $HCl-H_2O_2$ over a wide range of temperatures. At 30 °C, only 15% conversion was obtained in 4 h (Table 5). When the temperature was increased to 60 °C, the conversion of 4-methylbenzenesulphonic acid increased to 82%. However, a further increase in temperature from 60 to 80 °C decreased the conversion level from 82% to 54%. 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 the higher temperature.

Effect of Molar Ratio of Reactant:Hydrogen Peroxide. From stoichiometry, to form 1 mol of dichloro compound, 2 mol of hydrogen peroxide and 2 mol of hydrochloric acid are needed for 1 mol of reactant. In all the reactions carried out, hydrochloric acid was used at 5 mol/mol to ensure maximum utilization of hydrogen peroxide to form chlorine. The mole ratio of 4-methylbenzenesulphonic acid to hydrogen peroxide was varied from 1.0:1.0 to 1.0:2.5 (Table 6). It was observed that, when only half of the theoretical amount of hydrogen peroxide was used, 68% conversion of 4-methylbenzenesulphonic acid was achieved. The selectivity with respect to the monochloro compound was as high as 92%. When the mole ratio was increased to 1.0:2.2, the conversion increased to 82%, and the selectivity with respect to the desired dichloro compound also increased from 8% to 96%. There was hardly any increase in conversion when the mole ratio was increased further to 1.0:2.5.

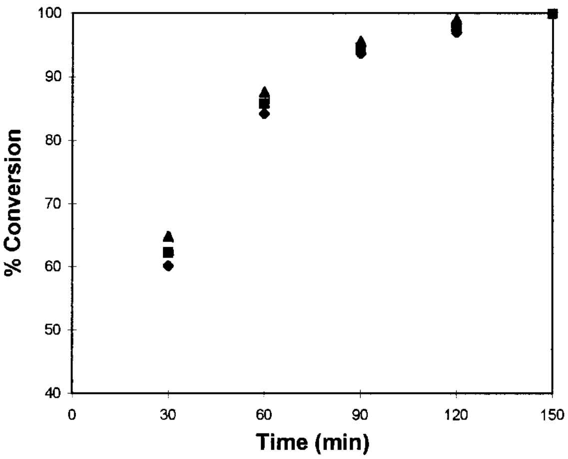

Figure 1. **Rate of desulphonation of DCMBSA. Reaction conditions: temperature, 210 °C; sulphuric acid, 70% w/v; reaction volume, 50 mL. Key to symbols (% w/v): ◆, 10; ■, 15; ▲, 20.**

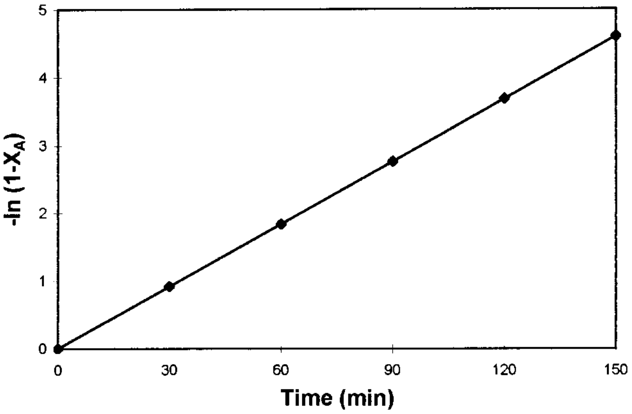

Figure 2. **First-order rate plot for desulphonation of DCMBSA. Reaction conditions: initial concentration, 10% w/v; temperature, 210 °C; sulphuric acid, 70% w/v; reaction volume, 50 mL.**

Desulphonation of DCMBSA. *Effect of Concentration of DCMBSA.* The rate of desulphonation was almost the same when the initial reactant concentration was increased from 10% to 20% w/v (Figure 1). A plot of $-\ln(1 - X_A)$ vs time, t (Figure 2), shows that the reaction is first order with respect to DCMBSA.

Effect of Temperature on Rate of Desulphonation. Desulphonation of 4-methylbenzenesulphonic acid was studied over a temperature range of 150−220 °C (Figure 3). A reaction temperature of 210 °C proved to be most suitable for this reaction. Temperature above 210 °C increased the rate of reaction but decreased the selectivity due to the formation of some tarry material. From the Arrhenius plot (Figure 4), the energy of activation was found to be 23.7 kcal/mol.

Effect of Sulphuric Acid Concentration on Rate of Desulphonation. The concentration of sulphuric acid plays an important role in this type of reaction. Thus, the effect

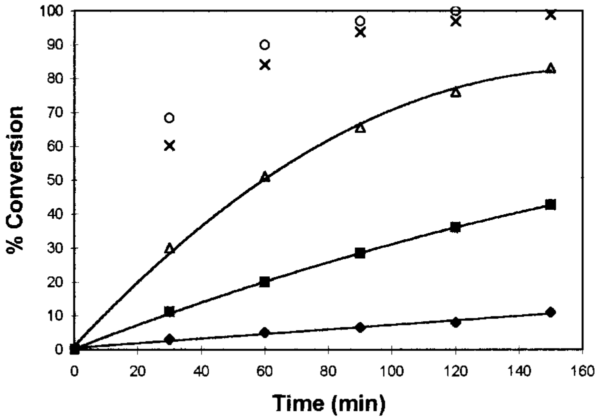

Figure 3. **Effect of temperature on rate of desulphonation of DCMBSA. Reaction conditions: initial concentration, 10% w/v; sulphuric acid, 70% w/v; reaction volume, 50 mL. Key to symbols (°C): ◆, 150; ■, 170; △, 190; ×, 210; ○, 220.**

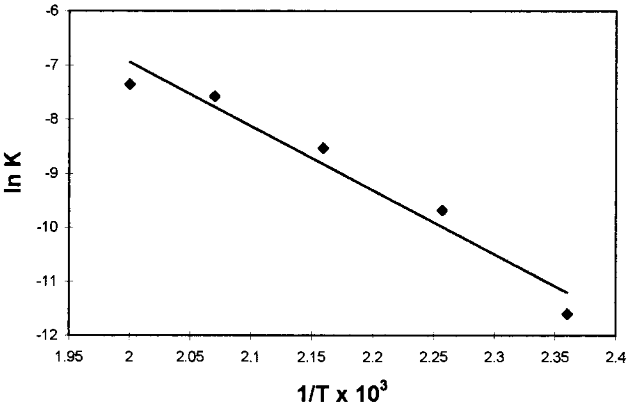

Figure 4. **Arrhenius plot for the desulphonation of DCMBSA. Reaction conditions: initial concentration, 10% w/v; sulphuric acid, 70% w/v; reaction volume, 50 mL.**

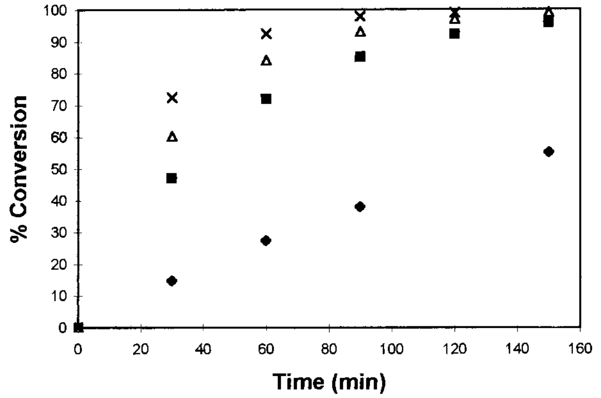

Figure 5. **Effect of concentration of sulphuric acid on desulphonation of DCMBSA. Reaction conditions: initial concentration, 10% w/v; temperature, 210 °C; reaction volume, 50 mL. Key to symbols (% sulfuric acid): ◆, 50; ■, 60; △, 70; ×, 80.**

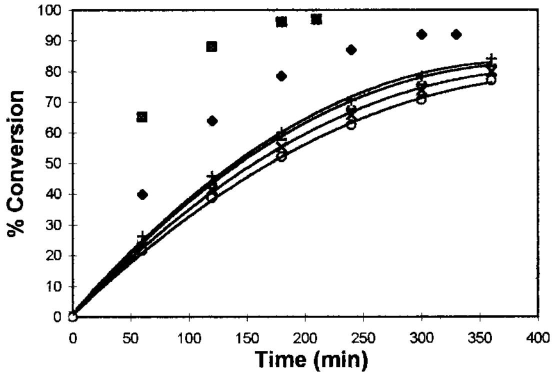

Figure 6. **Rate of thermal decarboxylation of benzoic acids. Reaction conditions: initial concentration, 10% w/v; temperature, 220 °C; catalyst, cuprous oxide; catalyst loading, 1% w/v; solvent, quinoline; reaction volume, 50 mL. Key to symbols: ◆, benzoic acid; ■, nitrobenzoic acid; △, 4-methylbenzoic acid; ×, 3,5-dichloro-4-aminobenzoic acid; +, 3,5-dichloro-4-hydroxybenzoic acid; ○, 3,5-dichloro-4-methylbenzoic acid.**

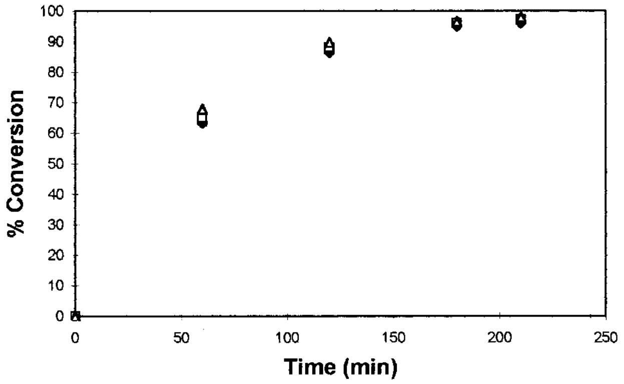

Figure 7. **Decarboxylation of 4-nitrobenzoic acid: effect of initial concentration on overall conversion. Reaction conditions: temperature, 220 °C; catalyst, cuprous oxide; catalyst loading, 1% w/v; solvent, quinoline; reaction volume, 50 mL. Key to symbols (% w/v): ◆, 5; □, 10; △, 15.**

of different concentrations of sulphuric acid ranging from 50% to 80% w/v on the rate of desulphonation was studied (Figure 5). It was observed that, at 50% concentration of sulphuric acid, the apparent rate of reaction was very slow: only 14.8% conversion was achieved. When the concentration was increased to 70%, 60.2% conversion was obtained. A further increase in concentration increased the conversion but decreased the selectivity with respect to the product. It was observed that 70% sulphuric acid was most suitable for this reaction.

Decarboxylation of Benzoic Acids. *Effect of Different Reactants on Overall Conversion.* Different reactants such as benzoic acid, 4-nitrobenzoic acid, 4-methylbenzoic acid, 3,5-dichloro-4-aminobenzoic acid, 3,5-dichloro-4-hydroxybenzoic acid, and 3,5-dichloro-4-methylbenzoic acid were used to study the rate of decarboxylation. Among these compounds, 4-nitrobenzoic acid readily decarboxylated under the reaction conditions. The rate of decarboxylation of 3,5-dichloro-4-methylbenzoic acid was very slow (Figure 6).

To study the different parameters for this reaction, 4-nitrobenzoic acid was used as a model compound.

Effect of Reactant Concentration on the Rate of Decarboxylation. The initial concentration of the reactant had very little effect on the rate of reaction. At 5% reactant concentration, 86.5% conversion was obtained in 2 h. When the reactant concentration was increased to 15%, 89.5% (Figure 7) conversion was obtained in 2 h. This indicates that the reaction is first order with respect to the reactant. A plot of $-\ln(1 - X_A)$ vs t proved this (Figure 8).

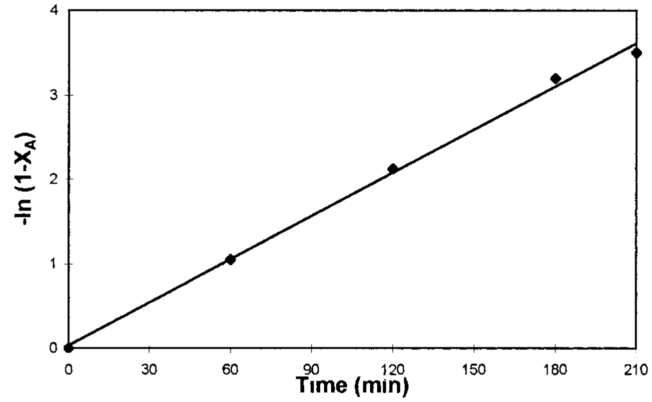

Figure 8. **First-order rate plot for decarboxylation of 4-nitrobenzoic acid. Reaction conditions: initial concentration, 10% w/v; temperature, 220 °C; catalyst, cuprous oxide; catalyst loading, 1% w/v; solvent, quinoline; reaction volume, 50 mL.**

Table 7. **Effect of catalyst on the decarboxylation of 4-nitrobenzoic acid**[a]

catalyst	overall conversion (%)	selectivity (%)
cuprous oxide	97	98
cupric oxide	39	95
none	16	96

[a] Reaction conditions: initial reactant concentration, 10% w/v; temperature, 220 °C; reaction time, 3 h; catalyst loading, 1% w/v; reaction volume, 50 mL.

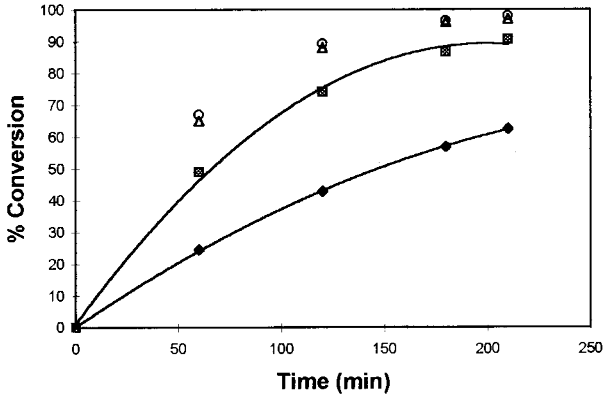

Figure 9. **Rate of decarboxylation of 4-nitrobenzoic acid vs catalyst loading. Reaction conditions: initial concentration, 10% w/v; temperature, 220 °C; catalyst, cuprous oxide; solvent, quinoline; reaction volume, 50 mL. Key to symbols (% w/v): ◆, 0.5; ■, 0.75; △, 1.0; ○, 1.25.**

Effect of Type and Loading of Catalyst on Rate of Decarboxylation. Catalyst loading played an important role in the rate of decarboxylation. Cuprous oxide and cupric oxide were taken as catalyst. It was observed that the rate of decarboxylation was much faster when cuprous oxide was taken as catalyst (Table 7).

To study the effect of catalyst loading on the rate of decarboxylation, the reaction was studied over a range of 0−1.25% w/v catalyst loading (Figure 9). It was observed that 1% catalyst loading was most suitable under the reaction conditions.

From Figure 10, it can be easily seen that the initial rate of decarboxylation of 4-nitrobenzoic acid increased rapidly when the catalyst loading increased from 0 to 1% w/v. The conversion leveled off at a catalyst loading of 1% or above.

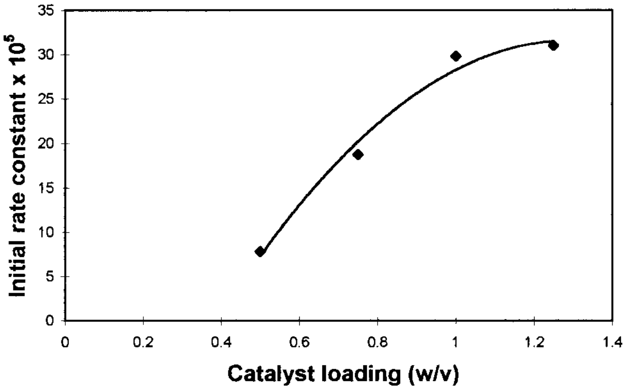

Figure 10. **Initial rate in the decarboxylation of 4-nitrobenzoic acid. Reaction conditions: initial concentration, 10% w/v; temperature, 220 °C; time, 3 h; catalyst, cuprous oxide; solvent, quinoline; reaction volume, 50 mL.**

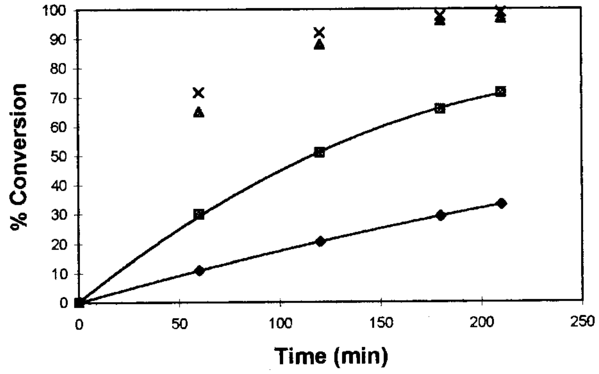

Figure 11. **Rate of decarboxylation of 4-nitrobenzoic acid vs temperature. Reaction conditions: initial concentration, 10% w/v; catalyst loading, 1% w/v; solvent, quinoline; catalyst, cuprous oxide; reaction volume, 50 mL. Key to symbols (°C): ◆, 160; ■, 190; ▲, 220; ×, 225.**

Effect of Temperature on Rate of Decarboxylation. At 160 °C, only 20.6% conversion was obtained in 2 h (Figure 11). When the temperature was increased to 220 °C, 88% conversion was obtained in only 2 h of reaction time. A further increase in temperature decreased the selectivity due to the formation of some tarry material. When *N,N*-dimethylaniline was used as a solvent, high temperature could not be used as *N,N*-dimethylaniline is susceptible to dealkylation at temperatures of 230−235 °C. Therefore, the reaction was carried out at 220 °C whenever *N,N*-dimethylaniline was used as the solvent.

From the Arrhenius plot, the energy of activation was found to be 16.2 kcal/mol (Figure 12).

Effect of Solvent on Rate of Decarboxylation. 70% sulphuric acid, water, quinoline, and *N,N*-dimethylaniline were used as solvents for this study. It was observed (Figure 13) that, in water, the rate of decarboxylation was very slow. The maximum rate was observed when 70% sulphuric acid or quinoline was used as the solvent. The selectivity was found to be very high when quinoline was used as the solvent. At 220 °C, the rate in *N,N*-dimethylaniline was much slower than that of quinoline, but the selectivity was almost the same. The separation of product from the

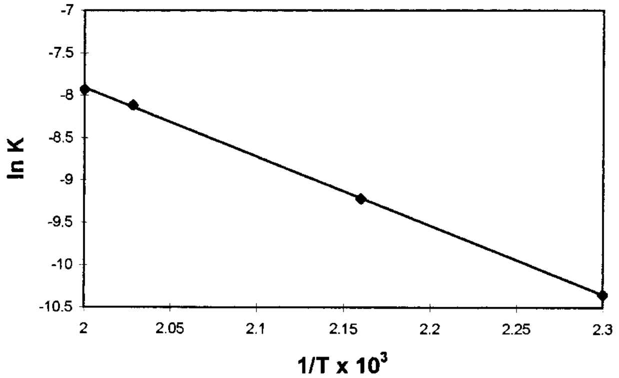

Figure 12. **Arrhenius plot for decarboxylation of 4-nitrobenzoic acid. Reaction conditions: initial concentration, 10% w/v; catalyst loading, 1% w/v; reaction volume, 50 mL.**

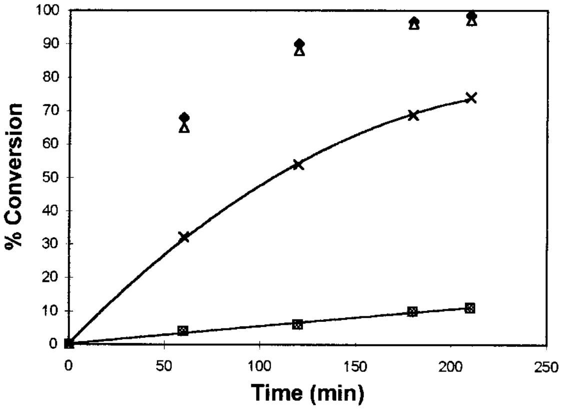

Figure 13. **Effect of solvent on decarboxylation of 4-nitrobenzoic acid. Reaction conditions: initial concentration, 10% w/v; temperature, 220 °C; catalyst, cuprous oxide; catalyst loading, 1% w/v; reaction volume, 50 mL. Key to symbols: ◆, 70% w/v sulphuric acid; ■, water; △, quinoline; ×, *N,N*-dimethylaniline.**

unreacted acid was much easier in *N,N*-dimethylaniline.

Optimum Conditions and Isolated Yields. *(i) 2,6-Dichlorotoluene.* 2,6-Dichlorotoluene was prepared by (i) oxidative chlorination of 4-methylbenzenesulphonic acid followed by desulphonation or (ii) oxidative chlorination of 4-methylbenzoic acid and followed by decarboxylation.

As 4-methylbenzenesulphonic acid is a less expensive starting material, the optimum conditions are given for the process scheme starting with this raw material.

Oxidative Chlorination of 4-Methylbenzenesulphonic Acid. Conditions: reactant concentration, 0.87 gmol/L; hydrochloric acid, 4.38 gmol/L; hydrogen peroxide, 1.914 gmol/L; reaction temperature, 60 °C; reaction time, 4 h. Overall conversion of 4-methylbenzenesulphonic acid: 78%. Selectivity with respect to dichloro compound: 96%. Conversion to monochloro compound: 1.5%. Tarry material: 1.65%. Isolated yield: 71%.

Desulphonation of 3,5-Dichloro-4-methylbenzenesulphonic Acid. Conditions: concentration of DCMBSA, 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. Overall conversion of dichlorobenzenesulphonic acid: 100%. Selectivity with respect to 2,6-dichlorotoluene: 97%. Conversion to monochlorotoluene: 1.1%. Tarry material: 1.4%. Isolated yield: 93%. The overall isolated yield of 2,6-dichlorotoluene on the basis of 4-methylbenzesulphonic acid was 66%.

(ii) 2,6-Dichloroaniline. Oxidative Chlorination of 4-Aminobenzoic Acid. Conditions: reactant concentration, 0.87 gmol/L; hydrochloric acid, 4.38 gmol/L; hydrogen peroxide, 1.914 gmol/L; reaction temperature, 60 °C; solvent, acetic acid; reaction time, 4 h. Overall conversion of 4-aminobenzoic acid: 68%. Selectivity with respect to dichloro compound: 93%. Conversion to monochloro compound: 2.3%. Tarry material: 2.7%. Isolated yield: 60%.

Decarboxylation of 3,5-Dichloro-4-aminobenzoic Acid. Conditions: Reactant concentration, 10% w/v; temperature, 220 °C; catalyst, cuprous oxide; catalyst loading, 1% w/v; solvent, quinoline; reaction time, 6 h. Overall conversion of 3,5-dichloro-4-aminobenzoic acid: 91%. Selectivity with respect to 2,6-dichloroaniline: 96%. Tarry material: 3.0%. Isolated yield: 85%. The overall isolated yield of 2,6-dichloroaniline on the basis of 4-aminobenzoic acid was 51%.

(iii) 2,6-Dichlorophenol. Oxidative Chlorination of 4-Hydroxybenzoic Acid. Conditions: reactant concentration, 0.87 gmol/L; hydrochloric acid, 4.38 gmol/L; hydrogen peroxide, 1.914 gmol/L; reaction temperature, 60 °C; solvent, acetic acid; reaction time, 4 h. Overall conversion of 4-hydroxybenzoic acid: 76%. Selectivity with respect to dichloro compound: 96%. Conversion to monochloro compound: 1.3%. Tarry material: 2.7%. Isolated yield: 68%

Decarboxylation of 3,5-Dichloro-4-hydroxybenzoic Acid. Conditions: reactant concentration, 10% w/v; temperature, 220 °C; catalyst, cuprous oxide; catalyst loading, 1% w/v; solvent, quinoline; reaction time, 6 h. Overall conversion of 3,5-dichloro-4-hydroxybenzoic acid: 90%. Selectivity with respect to 2,6-dichlorophenol: 97%. Tarry material: 2.1%. Isolated yield: 86%.The overall isolated yield of 2,6-dichlorophenol on the basis of 4-hydroxybenzoic acid was 58%.

Comparison of the Efficiency of the New Processes with the Existing Processes. 2,6-Dichlorotoluene can be prepared by chlorination of 4-methylbenzenesulphonyl chloride or 4-*tert*-butyltoluene followed by desulphonation or dealkylation. In this process scheme, 2,6-dichlorotoluene has been prepared by oxidative chlorination of 4-methylbenzenesulphonic acid followed by desulphonation. It is more convenient to start with an easily available and less expensive raw material than to start with a costly raw material like 4-*tert*-butyltoluene. As the selectivity towards the desired product obtained in this process scheme was very high, the separation was easier than with the existing processes. There is no need to use costly solvents for selective chlorination. A less expensive solvent like water or acetic acid was used in this investigation. The homogeneiety of the reaction mixture was an added advantage for this process scheme, in that the rate of raection was higher than those for the processes described in the literature. The isolated yields of 2,6-dichlorotoluene, 2,6-dichloroaniline, and 2,6-dichlorophenol were also very high.

Conclusions

It has been shown that some important organic intermediates can be prepared by a protection and deprotection 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 chloro-substituted aromatic intermediates in high selectivity.

In the oxidative chlorination, the selectivity towards the dichloro compounds was very high. Only 1−3% of monochloro compound and 1−2% of tarry material were formed as byproducts under the best suitable conditions.

Formation of mono- or dichloro compounds can be controlled by manipulating the molar ratio of hydrogen peroxide to the reactant, keeping the hydrochloric acid in excess.

Desulphonation of 3,5-dichloro-4-methylbenzenesulphonic acid was successfully performed to obtain 2,6-dichlorotoluene in high yield, and the reaction follows first-order kinetics. The energy of activation was found to be 23.7 kcal/mol.

Decarboxylation of 3,5-dichloro-4-methylbenzoic acid, 3,5-dichloro-4-aminobenzoic acid, and 3,5-dichloro-4-hydroxybenzoic acid was successfully performed to obtain 2,6-dichlorotoluene, 2,6-dichloroaniline, and 2,6-dichlorophenol in good yield. It was observed that decarboxylation of 4-nitrobenzoic acid follows first-order kinetics, and detailed parameter studies enabled definition of optimum reaction conditions. The energy of activation was found to be 16.2 kcal/mol.

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

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