Organic Process Research & Development **1999**, *3*, 451–454

Oxidative Bromination in a Liquid−Liquid Two-Phase System to Synthesize Organic Intermediates: 2-Bromophenol, 2,6-Dibromophenol, and 2-Bromo-4-methylphenol

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Abstract:

An alternative manufacturing process-scheme was developed to synthesize 2-bromophenol and 2,6-dibromophenol involving oxidative bromination of a substrate protected in the para position in a two-phase system followed by deprotection involving decarboxylation. Thus, selective oxidative bromination of 4-hydroxybenzoic acid in ethylenedichloride with HBr−H_2O_2, and subsequent decarboxylation in quinoline gave 90−95% yield to the mono- or dibromophenol depending upon the mol ratio of HBr:H_2O_2 employed in the oxidative bromination. Similarly, 4-methylphenol under identical reaction conditions gave 99.6% selectivity to 2-bromo-4-methylphenol at 89% conversion ratio of 4-methylphenol.

Introduction

2-Bromophenol, 2,6-dibromophenol, and 2-bromo-4-methyl phenol have great relevance in organic process industries as intermediates for fine-chemicals and pharmaceuticals. In general, these are synthesized by direct bromination of the reactant. But there is always a chance of getting an isomeric mixture[1,2] of 2- and 4-halo substituted products with some di- or trihalo compounds from which, the separation of the desired product itself is a problem. Oxidative halogenation by using HCl or HBr and H_2O_2 of a para-blocked substrate followed by deprotection involving desulphonation or decarboxylation is reported.[3−5] 2,6-Dibromophenol has been produced by bromination of 4-hydroxybenzoic acid and subsequent decarboxylation.[6−7] The above halogenations were carried out in homogeneous conditions or in aqueous acidic solution, where the separation of the desired product from the highly corrosive aqueous hydrochloric or hydrobromic acid solution is a major problem. In this work, oxidative bromination is done in a liquid−liquid two-phase system to get an easy and environmentally friendly separation of the desired product from the reaction mixture. 4-Hydroxybenzoic acid and 4-methylphenol were brominated selectively by using HBr−H_2O_2 in a two-phase system, and the resultant bromocarboxylic acids, in case of 4-hydroxybenzoic acid, were decarboxylated in quinoline to obtain the products. In case of 4-methylphenol after the oxidative bromination, the product was isolated by fractional distillation. (Scheme 1).

Experimental Section

Oxidative Bromination. *Experimental Procedure.* The experiments were carried out in a 250-mL borosilicate glass reactor equipped with 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. For large-scale industrial production, it is worth considering the use of a glass- or titanium-lined reactor.

In a typical reaction, 0.0435 mol of substrate and 0.174 mol of 40% hydrobromic acid were added to 50 mL of ethylenedichloride, and the reaction mixture was kept at 45 °C. Then, 0.039 mol of 30% hydrogen peroxide was added dropwise to the reaction mixture over 2.5 h. The reaction mixture was stirred for another 0.5 h at 45 °C. The layers were separated when the reaction was over. In the case of 4-methylphenol, the product, 2-bromo-4-methylphenol, was isolated by fractionation of the organic layer (isolated yield, 97%; bp, 109−114 °C at 29−31 mm), but in the case of 4-hydroxybenzoic acid, the products, 3-bromo-4-hydroxybenzoic acid or 3,5-dibromo-4-hydroxybenzoic acid, were isolated by distilling out the organic solvent under atmospheric pressure. The acids were then dried and taken for the decarboxylation step. The decarboxylation mixture was distilled under reduced pressure to isolate 2-bromophenol (isolated yield, 88%; bp, 93−97 °C at 31−32 mm) and 2,6-dibromophenol (isolated yield, 92%; bp, 174−178 °C at 30−33 mm).

Analytical Procedure. The reaction mixture was analyzed by HPLC. Column used: MERCK50983, Lichrosphere 100 RP-18, 5 μm. 254 × 4 mm.

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

Decarboxylation. *Experimental Procedure.* A 100-mL autoclave was used for the decarboxylation reactions. In a typical reaction, 5 g of bromo-substituted benzoic acid, 0.5 g of cuprous oxide, and 50 mL of quinoline were charged

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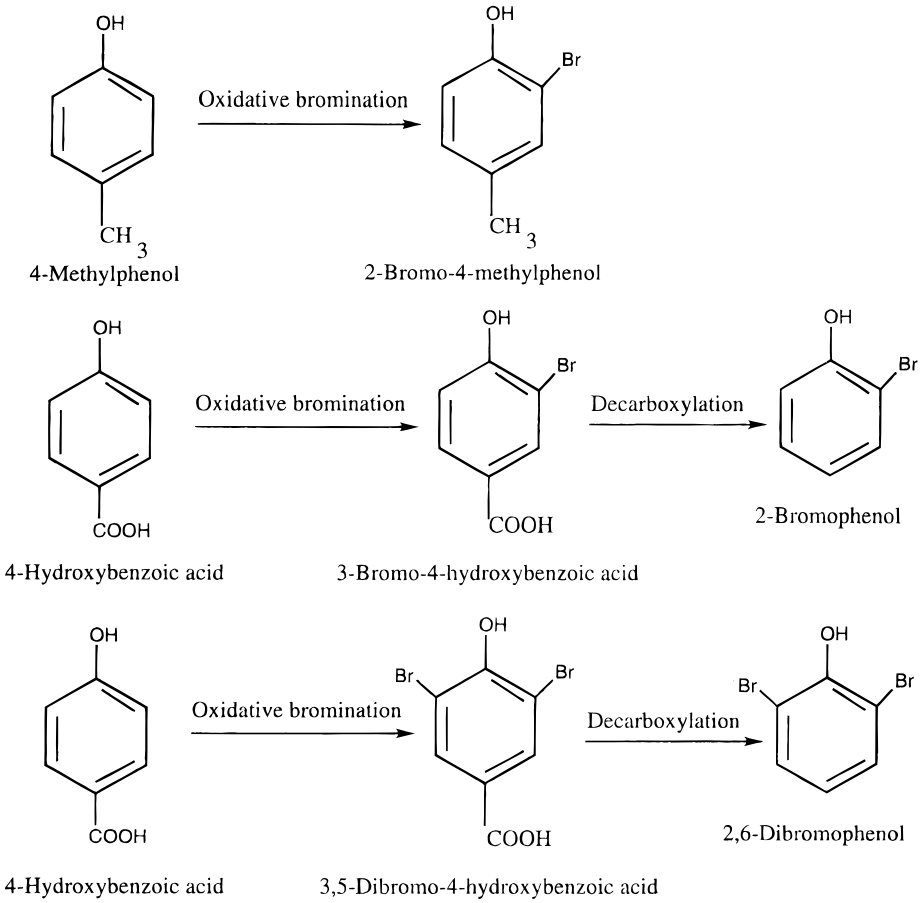
10.1021/op990035n CCC: $18.00
Published on Web 11/02/1999

Scheme 1. **Oxidative bromination of 4-methylphenol and 4-hydroxybenzoic acid**



into the autoclave. The autoclave was heated to 220 °C and kept for 6 h at 1000 rpm speed of agitation. After the reaction was over, the reaction mixture was cooled and filtered to remove the catalyst. The filtrate was distilled under vacuum using a 2-m wire mesh packed column to isolate the bromo compound, (purity > 98.5%).

Analytical Procedure. Samples (1−2 mL) were withdrawn after regular intervals of time and were analyzed by GC as well as HPLC. Standard compounds were used for external calibrations.

GC Conditions: Column used, 2m SE−30 on chromosorb-W; carrier gas, nitrogen; flow rate, 30 mL/min; injector temperature, 300 °C; detector temperature, 300 °C; oven temperature, 100 °C, 1 min, 8 °C/min, 220 °C, 15 °C/min, 250 °C, 5 min.

Results and Discussion

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

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

Oxidative Bromination. *Batch Mode vs Semibatch Mode.* To determine the most suitable conditions for maximum conversion and selectivity, the oxidative bromination of 4-methylphenol was studied in batch mode as well as semibatch mode. In batch mode, all of the H_2O_2 was added at once in to the reactor initially, whereas, in semibatch mode, H_2O_2 was added dropwise to the reaction mixture over a specified time period. It was observed that when hydrogen peroxide was added dropwise, the conversion and selectivity were 89 and 99.6%, compared to 59 and 68% respectively, when the reaction was done in a batchmode (Table 1).

Table 1. **Oxidative bromination of 4-methylphenol: effect of mode of reaction[a]**

mode of addition	% overall conversion	% selectivity
batch mode	59	68
semi-batch mode	89	99.6

[a] Reaction conditions: reactant concentration, 0.87 mol/L of organic phase; hydrobromic acid, 3.48 mol/L of aqueous phase; hydrogen peroxide, 0.783 mol/L of aqueous phase; temperature, 45 °C; organic phase, 50 mL; reaction time, 3 h.

Effect of Addition Time of Hydrogen Peroxide. With an increase in addition time, the overall conversion of 4-methylphenol also increased (Table 2). Thus, to get maximum selectivity and utilization of hydrogen peroxide, a 2.5 h addition time was preferred under these reaction conditions.

Effect of Different Substrate on Rate and Selectivity. Under identical reaction conditions though, the rate of oxidative bromination of 4-methylphenol was faster than that of 4-hydroxy benzoic acid but selectivity remained almost the same (Table 3).

Table 2. **Oxidative bromination of 4-methylphenol: effect of addition time of hydrogen peroxide[a]**

addition time, h	% overall conversion	% selectivity to monobromo compound
1.0	57	81
1.5	68	92
2.0	76	95
2.5	89	99.6
3.0	89	99.8

[a] Reaction conditions: initial reactant concentration, 0.87 mol/L of organic phase; hydrobromic acid, 3.48 mol/L of aqueous phase; hydrogen peroxide, 0.783 mol/L of aqueous phase; organic phase, 50 mL; temperature, 45 °C; reaction time including addition time, 3 h.

Table 3. **Oxidative monobromination of different substrate[a]**

reactant	% overall conversion	% selectivity to monobromo compound
4-methylphenol	89	99.6
4-hydroxy-benzoic acid	81	99

[a] Reaction conditions: reactant concentration, 0.87 mol/L; hydrobromic acid, 3.48 mol/L; hydrogen peroxide, 0.783 mol/L; ethylenedichloride, 50 mL; temperature, 45 °C; reaction time, 3 h.

Table 4. **Oxidative bromination of 4-methylphenol in different organic solvent[a]**

solvent	overall conversion (%)	selectivity (%)
ethylenedichloride	89	99.6
carbontetrachloride	86	99
chloroform	89.4	99.8
1,1,1-trichloroethane	88	99.5

[a] Reaction conditions: reactant concentration, 0.87 mol/L; hydrobromic acid, 3.48 mol/L; hydrogen peroxide, 0.783 mol/L; temperature, 45 °C; organic phase, 50 mL; reaction time, 3 h.

Effect of Solvent on the Rate and Selectivity of Oxidative Bromination. The rate of oxidative bromination of 4-methylphenol was examined in four different solvents, ethylenedichloride, carbon tetrachloride, chloroform, and 1,1,1-trichloroethane. It was observed that the rate and selectivity were almost same for these solvents under the reaction conditions (Table 4). All of the subsequent runs were performed in ethylenedichloride.

Effect of Temperature on the Rate of Oxidative Bromination of 4-Methylphenol. The oxidative bromination of 4-methyphenol was studied by using $HBr-H_2O_2$ over a wide range of temperatures. At 20 °C only 17% conversion was obtained in 3 h (Table 5). When the temperature was increased to 45 °C, the conversion of 4-methylphenol increased to 89%. However, a further increase in temperature from 45 to 55 °C decreased the conversion level from 89 to 71%. This is due to the rate of decomposition of hydrogen peroxide being much faster than the rate of reaction of hydrogen peroxide with hydrobromic acid at the higher temperature. The selectivity was as high as 100% up to 45 °C, but at 55 °C, the selectivity decreased to 82%; this is due to the higher overall rate of reaction at higher temperatures, leading to dibromo and residue formation.

Table 5. **Effect of temperature on the rate and selectivity of oxidative bromination of 4-methylphenol[a]**

temperature (°C)	overall conversion (%)	selectivity (%)
20	17	100
30	46	100
45	89	99.7
55	71	82

[a] Reaction conditions: reactant concentration, 0.87 mol/L of organic phase; hydrobromic acid, 3.48 mol/L of aqueous phase; hydrogen peroxide, 0.783 mol/L of aqueous phase; organic phase, 50 mL; reaction time, 3 h.

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

reactant:H_2O_2	overall conversion (%)	selectivity to monobromo cmpd (%)	selectivity to dibromo cmpd (%)
1:0.5	47	100	0
1:0.9	89	99.6	0.3
1:1	93	95	4.5
1:1.5	95	72	27
1:2.0	98	8	91.3
1:2.1	98	0.5	99.2

[a] Reaction conditions: reactant concentration, 0.87 mol/L of organic phase; hydrobromic acid, 3.48 mol/L of aqueous phase; organic phase, 50 mL; temperature, 45 °C; reaction time, 3 h.

Table 7. **Optimum conditions and isolated yield with 100% material balance for the oxidative bromination of 4-methylphenol[a]**

overall conversion of 4-methylphenol	89%
selectivity with respect to monobromo compound	99.6%
conversion to dibromo compound	0.3%
tarry material	0.1%
isolated yield	97

[a] Reaction conditions: reactant concentration, 0.87 mol/L of organic phase; hydrobromic acid, 3.48 mol/L of aqueous phase; hydrogen peroxide, 0.783 mol/L of aqueous phase; organic phase, 50 mL; temperature, 45 °C; reaction time, 3 h.

Effect of Molar Ratio of Reactant:Hydrogen Peroxide on the Rate of Oxidative Bromination of 4-Methylphenol. From stoichiometry, to form one mole of monobromo compound, one mole of hydrogen peroxide and one mole of hydrobromic acid are needed for one mole of reactant. In all of the reactions carried out, hydrobromic acid was used at 4 mol/mol of reactant to ensure maximum utilization of hydrogen peroxide to form bromine. The mole ratio of 4-methylphenol to hydrogen peroxide was varied from 1.0:0.5 to 1.0:2.1 (Table 6). It was observed that when only 90% of the theoretical amount of hydrogen peroxide was used, 89% conversion of 4-methylphenol was achieved. The selectivity with respect to monobromo compound was as high as 99.6%. When the mole ratio was increased to 1.0:2.1, the selectivity with respect to the desired monobromo compound decreased from 99.6 to 0.5% due to a higher rate of formation of the dibromo compound. Thus, a ratio of 1.0:0.9 was found to be the most suitable for the synthesis of 2-bromo-4-

Table 8. **Optimum conditions for the oxidative monobromination of 4-hydroxybenzoic acid[a]**

overall conversion of 4-hydroxybenzoic acid	87%
selectivity with respect to monobromo compound	99%
selectivity to dibromo compound	0.4%
tarry material	0.6%
isolated yield	96%

[a] Reaction conditions: reactant concentration, 0.87 mol/L of organic phase; hydrobromic acid, 3.48 mol/L of aqueous phase; hydrogen peroxide, 0.783 mol/L of aqueous phase; temperature, 45 °C; organic phase, 50 mL; reaction time, 3 h.

Table 9. **Optimum conditions for the decarboxylation of 3-bromo-4-hydroxybenzoic acid to synthesize 2-bromophenol[a]**

overall conversion of 3-bromo-4-hydroxybenzoic acid	97%
selectivity with respect to 2-bromophenol	98%
tarry material	1.3%
isolated yield	92%
overall isolated yield to 2-bromophenol in two steps	88%

[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 10. **Optimum conditions for the oxidative dibromination of 4-hydroxybenzoic acid[a]**

overall conversion of 4-hydroxybenzoic acid	92%
selectivity with respect to dibromo compound	99%
conversion to monobromo compound	0.6%
tarry material	0.3%
isolated yield	97%

[a] Reaction conditions: reactant concentration, 0.87 mol/L of organic phase; hydrobromic acid, 3.48 mol/L of aqueous phase; hydrogen peroxide, 1.827 mol/L of aqueous phase; organic phase, 50 mL; temperature, 45 °C; reaction time, 3 h.

methylphenol and 3-bromo-4-hydroxybenzoic acid and a ratio of 1:2.1 for the synthesis of 3,5-dibromo-4-hydroxybenzoic acid.

Optimum Conditions. The optimum conditions with 100% material balance for all of the compounds are given in Tables 7 −11.

Comparison of the Efficiency of the New Processes with the Existing Processes. Direct bromination of cresols and phenols always ends up with byproducts and tarry material,

Table 11. **Optimum conditions for the decarboxylation of 3,5-dibromo-4- hydroxybenzoic acid to synthesize 2,6-dibromophenol[a]**

overall conversion of 3,5-di-bromo-4-hydroxybenzoic acid	99%
selectivity with respect to 2,6-dibromophenol	98%
tarry material	1.3%
isolated yield	95%
overall isolated yield to 2,6-dibromophenol in two steps	92%

[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.

which results in a very low selectivity to the desired products. In this process-scheme, 2-bromophenol and 2,6,-dibromophenol have been prepared by oxidative bromination of 4-hydroxybenzoic acid followed by decarboxylation. The selectivity towards the desired product obtained in this process-scheme was very high, a two-phase liquid−liquid system was employed, and the separation became very easy. A cheaper solvent, ethylenedichloride, was used in this investigation. The isolated yield of 2-bromophenol, 2,6-dibromophenol, and 2-bromo-4-methylphenol was much higher in comparison to the existing processes.

Conclusions

It has been shown that some important bromo-substituted organic intermediates can be prepared selectively by this method. Although direct bromination using liquid bromine is an industrial process, oxidative bromination could be considered as a potentially useful process to manufacture high-priced low-volume bromo-substituted aromatic intermediates in very high selectivity.

Decarboxylations of 3-bromo-4-hydroxybenzoic acid and 3,5-dibromo-4-hydroxybenzoic acid were successfully performed to obtain 2-bromo and 2,6-dibromophenol in very high yield.

Acknowledgment

Sudip and Ananthakrishnan are grateful to the University Grants Commissions, New Delhi, for the award of Senior Research Fellowship.

Received for review April 19, 1999.

OP990035N