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Oxidation of toluenes to benzoic acids by oxygen in non-acidic solvents

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Abstract—Oxidation of substituted toluenes by molecular oxygen at one atmosphere to the corresponding substituted benzoic acids in non-acidic solvents was investigated. Satisfactory oxidation of halo-, methoxy-, and cyano-toluenes were achieved using $Co(C_{18}H_{35}O_2)_2/NH_4Br$ or $Co(OAc)_2/NaBr/AcOH$ as catalysts in the presence of a radical initiator.

1. Introduction

Substituted benzoic acids are very important materials in chemical and pharmaceutical industries and can be prepared by oxidation of the corresponding substituted toluenes.[1–3] In recent years, oxidation processes with environmentally friendly oxidants have received much attention.[4–6] One of the most attractive oxidants is molecular oxygen. Normally, the oxidation with molecular oxygen is carried out in aliphatic acid medium, which causes corrosive and environmentally less-friendly problems.[7] Up to date, oxidation of substituted toluenes to the corresponding aromatic acids in non-acidic solvent has rarely been reported. Ishii and co-workers investigated the catalytic oxidation of alkylbenzenes with molecular oxygen by N-hydroxyphthalimide combined with $Co(OAc)_2$ in acetonitrile.[8] But the reaction conditions were unsatisfactory for substrates with electron-attracting groups. The oxidation of *p*-chlorotoluene gave only 40% yield, and no reaction was observed for *p*-nitrotoluene. Zhang et al. studied the oxidation of substituted toluenes with molecular oxygen in several organic solvents, such as acetonylacetone, 2-heptanone, nitrobenzene, DMF, acetonitrile, and butyl acetate with yield of 2%.[9] In this paper, we reported a new and effective method for oxidation of substituted toluenes with molecular oxygen under atmospheric pressure in non-acidic solvents, such as dichlorobenzene, chlorobenzene, and bromobenzene using $Co(C_{18}H_{35}O_2)_2/NH_4Br$ or $Co(OAc)_2/NaBr/AcOH$ as the catalyst in the presence of a radical initiator.

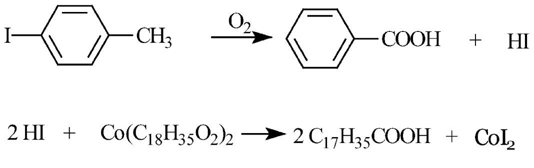
2. Results and discussion

The oxidation of halotoluenes, methoxytoluenes, cyanotoluenes and *p*-xylene with molecular oxygen under atmospheric pressure in halobenzene solvent was investigated, using $Co(C_{18}H_{35}O_2)_2/NH_4Br$ (system A) or $Co(OAc)_2/NaBr$ (system B) as the catalyst in the presence of a radical initiator, AIBN. The catalyst $Co(C_{18}H_{35}O_2)_2$ and the co-catalyst NH_4Br (system A) were more soluble in halobenzene. The results are listed in Table 1.

Among the halotoluenes (entries 1, 2, 3 and 4, Table 1) *p*-bromotoluene gave the best yield of 92% while only 32 and 66% were obtained for *p*-fluorotoluene and *p*-chlorotoluene, respectively. However, *p*-iodotoluene gave benzoic acid and stearic acid without any *p*-iodobenzoic acid formed. An explanation was illustrated in Scheme 1.

The oxidation of *p*-methoxytoluene gave good yield (88%, Table 1, entry 7). However, the substrate impurity must be purified to remove small amount of *p*-hydroxytoluene, which serves as the radical inhibitor.

The oxidation of *p*-xylene gave 96% yield of *p*-phthalic acid after 9 h while only *p*-toluic acid was observed in 2 h. These results were consistent with Digurov's result, which showed that the formation of *p*-phthalic acid commenced only after



Scheme 1.

Keywords: Oxidation; Toluenes; Benzoic acids; Oxygen.

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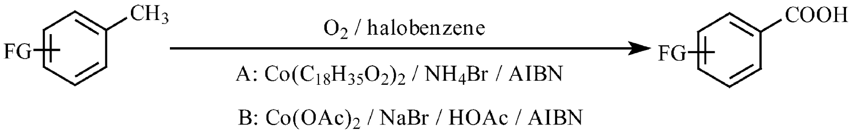
Table 1. Oxidation of substituted toluenes in halobenzene



Entry	Substrate	Solvent	Cat.[a]	Temp (°C)	Time (h)	Product	Yield[b] (%)
1	p-FC_6H_4Me	Dichlorobenzene	A	150	8	p-FC_6H_4COOH	32
2	p-ClC_6H_4Me	Dichlorobenzene	A	150	8	p-ClC_6H_4COOH	66
3	p-BrC_6H_4Me	Dichlorobenzene	A	150	8	p-BrC_6H_4COOH	92
4	p-IC_6H_4Me	Dichlorobenzene	A	150	8	p-IC_6H_4COOH	—[c]
5	p-$NO_2C_6H_4Me$	Dichlorobenzene	A	150	9	p-$NO_2C_6H_4COOH$	Trace
6	o-$NO_2C_6H_4Me$	Dichlorobenzene	A	150	9	o-$NO_2C_6H_4COOH$	Trace
7	p-$CH_3OC_6H_4Me$	Dichlorobenzene	A	150	4.5	p-$CH_3OC_6H_4COOH$	88
8	4-Cl-2-FC_6H_3Me	Dichlorobenzene	A	150	6	4-Cl-2-FC_6H_3COOH	85
9	p-$CH_3C_6H_4Me$	Dichlorobenzene	A	150	9	p-$HOOCC_6H_4COOH$	96
10	p-BrC_6H_4Me	Chlorobenzene	A	130	9	p-BrC_6H_4COOH	83
11	p-BrC_6H_4Me	Bromobenzene	A	150	9	p-BrC_6H_4COOH	90
12	p-FC_6H_4Me	Dichlorobenzene	B	110	8	p-FC_6H_4COOH	83
13	p-ClC_6H_4Me	Dichlorobenzene	B	110	8	p-ClC_6H_4COOH	84
14	p-BrC_6H_4Me	Dichlorobenzene	B	110	3	p-BrC_6H_4COOH	90
15	p-$NO_2C_6H_4Me$	Dichlorobenzene	B	110	9	p-$NO_2C_6H_4COOH$	67
16	o-$NO_2C_6H_4Me$	Dichlorobenzene	B	110	9	o-$NO_2C_6H_4COOH$	Trace
17	p-$CH_3OC_6H_4Me$	Dichlorobenzene	B	110	3	p-$CH_3OC_6H_4COOH$	94
18	4-Cl-2-FC_6H_3Me	Dichlorobenzene	B	110	5	4-Cl-2-FC_6H_3COOH	87
19	4-Br-2-FC_6H_3Me	Dichlorobenzene	B	110	4.5	4-Br-2-FC_6H_3COOH	91
20	p-CNC_6H_4Me	Chlorobenzene	B	110	2.5	p-CNC_6H_4COOH	96
21	m-CNC_6H_4Me	Chlorobenzene	B	110	3.5	m-CNC_6H_4COOH	87
22	o-CNC_6H_4Me	Chlorobenzene	B	110	7	o-CNC_6H_4COOH	31
23	p-$CH_3C_6H_4Me$	Dichlorobenzene	B	110	2	p-$CH_3C_6H_4COOH$	51
24	p-$CH_3C_6H_4Me$	Dichlorobenzene	B	110	9	p-$HOOCC_6H_4COOH$	92

[a] A: $Co(C_{18}H_{35}O_2)_2$ (6 mol%)/NH_4Br (5 mol%), 4 mol% AIBN; B: $Co(OAc)_2$ (5 mol%)/NaBr(3 mol%)/HOAc (50 mol%), 2 mol% AIBN.
[b] Isolated yield.
[c] Benzoic acid as the product.

p-tolualdehyde had been completely converted to *p*-toluic acid.[10]

Chlorobenzene and bromobenzene were also screened as solvents. Satisfactory yields were obtained (Table 1, entries 10 and 11).

The more common catalyst $Co(OAc)_2$ in the presence of catalytic amount of acetic acid (system B) was also examined. The results showed that almost all of the substrates were converted to the corresponding benzoic acids in higher yields at lower temperature (entries 12–24 in Table 1).

Cyano group is compatible with the reaction conditions (Table 1, entries 20, 21 and 22). However, the positions of substitution strongly influenced the yields. Up to 96 and 87% of isolated yields (entries 20 and 21) were obtained for *p*- and *m*-cyanobenzoic acids within about 3 h while only 31% of *o*-cyanobenzoic acid was achieved after 7 h. Meanwhile, *o*-nitrotoluene was not oxidized under these conditions. However, *p*-nitrotoluene led to *p*-nitrobenzoic acid in 67% yield.

The system B proved to be more efficient both in rate and yield. A lower temperature of 110 °C was required in system B compared to 150 °C in system A. The yields of *p*-fluorobenzoic acid and *p*-chlorobenzoic acid were improved greatly from 32 and 66% (Table 1, entries 1 and 2) to 83 and 84% (Table 1, entries 12 and 13), respectively. The possible reason was that hydrophilic acetic acid could promote the decomposing of intermediate $ArCH_2OOH$.[9]

When $Co(C_{18}H_{35}O_2)_2/NH_4Br$ or $Co(OAc)_2$/NaBr was used without any added radical initiator, no oxidation occurred. Radical initiators, such as AIBN, NHPI and benzoyl peroxide, were carried out under same conditions using *p*-bromotoluene as the substrate. The all exhibited the same activity at 150 °C while benzoyl peroxide was not effective at all at 110 °C (Table 2).

4-Chloro-2-fluorobenzoic acid and 4-bromo-2-fluorobenzoic acid are important pharmaceutical agents,[11,12] and were obtained in high yields (Table 1, entries 8, 18 and 19).

Table 2. Comparison of the efficiency of NHPI, $(C_6H_5CO_2)_2$ and AIBN[a]

Entry	Initiator	Cat.[b]	Temp (°C)	Time (h)	Yield[c] (%)
1	AIBN	A	150	9	92
2	$(C_6H_5CO_2)_2$	A	150	9	92
3	NHPI	A	150	9	95
4	AIBN	B	110	3	90
5	$(C_6H_5CO_2)_2$	B	110	3	Trace
6	NHPI	B	110	3	92

[a] *p*-Bromotoluene (15 mmol) was used as substrate.
[b] A: $Co(C_{18}H_{35}O_2)_2$ (6 mol%)/NH_4Br (5 mol%), 4 mol% of radical initiator; B: $Co(OAc)_2$ (5 mol%)/NaBr (3 mol%)/HOAc (50 mol%), 2 mol% of radical initiator.
[c] Isolated yield.

The mechanism for the aerobic oxidation of substituted toluenes catalyzed by cobalt(II) compounds has been proposed.[7,10,13,14] It is suggested that Co(II) reacts with dioxygen to generate a liable dioxygen complex of superoxocobalt(III) or μ-peroxocobalt(III) complex. These cobalt-oxygen species, which were reported to be easily formed by the one-electron reduction of dioxygen using cobalt(II),[15,16] assist the generation of the radical from AIBN at high temperature. Bromide, a promoter, may form Br· radical at low catalyst concentration to initiate the reaction.[10]

In conclusion, we have developed a practical procedure for the catalytic oxidation of substituted toluenes to corresponding aromatic acids in non-acidic solvent of halobenzenes under atmospheric pressure in the presence of a radical initiator. It is noteworthy that the reaction systems are applicable for the oxidation of both electron-withdrawing and electron-donating substituted toluenes.

3. Experimental

3.1. General remarks

Melting points were measured with a Yanaco Mp 500 apparatus. ^{1}H NMR spectra were recorded on a Bruker DRX-300 MHz spectrometer with tetramethylsilane as the internal standard.

3.2. General procedure

Substituted toluene, catalysts, radical initiator, and halobenzene were added to a three-necked flask with a reflux condenser. The mixture was heated, with oxygen bubbling through the solution for 3–10 h. After the reaction was finished, the mixture was cooled to room temperature, and crystals precipitated. Then crude product was obtained by filtration and further purified by recrystallization with ethanol/water. The yields of acids were 32–96%.

3.3. Typical procedure

3.3.1. Typical procedure for the oxidation of *p*-bromotoluene in catalyst system A. *p*-Bromotoluene (2.56 g, 15 mmol), AIBN (0.098 g, 0.6 mmol), $Co(C_{18}H_{35}O_2)_2$ (0.557 g, 0.9 mmol), and dichlorobenzene (20 mL) were added to a three-necked flask with a reflux condenser, and the mixture was heated at 150 °C, then oxygen was bubbled through the solution for 9 h. After the reaction was finished, the mixture was cooled to room temperature and *p*-bromobenzoic acid was precipitated. The crude product (2.71 g) was purified by recrystallization with ethanol/water, mp 251–252 °C [lit.[17] 251–253 °C]. The yield was 92%.

3.3.2. Typical procedure for the oxidation of *p*-methoxytoluene in catalyst system B. *p*-Methoxytoluene (2 g, 16.4 mmol), AIBN (0.081 g, 0.4 mmol), $Co(OAc)_2{\cdot}4H_2O$ (0.204 g, 0.8 mmol), NaBr (0.056 g, 0.54 mmol), HOAc (0.49 g, 8.2 mmol) and dichlorobenzene (10 mL) were added to a three-necked flask fitted with a reflux condenser. The mixture was heated to 110 °C with oxygen bubbling through the solution for 3 h. After the reaction was finished, the mixture was cooled to room temperature and *p*-methoxybenzoic acid was precipitated. The crude product was recrystallized with ethanol/water. Then 2.3 g of *p*-methoxybenzoic acid was obtained and the yield was 94%, mp 183–184 °C [lit.[18] 184 °C].

3.3.3. *p*-Fluorobenzoic acid. 4-Fluorotoluene was oxidized to give 4-fluorobenzoic acid as a white solid, mp 184–186 °C [lit.[19] 185 °C].

3.3.4. *p*-Chlorobenzoic acid. Oxidation of 4-chlorotoluene gave 4-chlorobenzoic acid as a white solid, mp 240–242 °C [lit.[20] 243 °C].

3.3.5. Cyanobenzoic acid (*p*-, *m*-, *o*-). *p*-Cyanotoluene, *m*-cyanotoluene and *o*-cyanotoluene were oxidized with molecular oxygen catalyzed by system B to give *p*-cyanobenzoic acid, *m*-cyanobenzoic acid and *o*-cyanobenzoic acid as white solids, respectively. *p*-Cyanobenzoic acid: mp 217–218 °C [lit.[21] 219 °C]; *m*-cyanobenzoic acid: mp 215–216 °C [lit.[21] 217 °C]; *o*-cyanobenzoic acid: mp 187–188 °C [lit.[22] 187 °C].

3.3.6. *p*-Phthalic aid. Oxidation of *p*-xylene catalyzed by system A gave *p*-phthalic aid as a white solid, 96% yield. Sublimes without melting at ca. 300 °C [lit.[23]].

3.3.7. *p*-Toluic acid. Oxidation of *p*-xylene catalyzed by system B gave *p*-phthalic aid as a white solid, 51% yield, mp 180–181 °C [lit.[24] 181 °C].

3.3.8. 4-Chloro-2-fluorobenzoic acid. White solid, mp 207–210 °C (C_2H_5OH/H_2O); δ_H (300 MHz, CD_3COCD_3) 7.9–8.0 (1H, m, ArH), 7.4–7.6 (2H, m, ArH).

3.3.9. 4-Bromo-2-fluorobenzoic acid. White solid, mp 237–240 °C (C_2H_5OH/H_2O); δ_H (300 MHz, CD_3COCD_3) 8.0–8.1 (1H, m, ArH), 7.6–7.8 (2H, m, ArH).

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