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ORIGINAL PAPER

The Cu(I)- and HNO_3-catalyzed oxidation of substituted toluenes to the benzoic acid based on NO_x recycling

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Abstract Based on the recycling of NO_x, the Cu(I)- and HNO_3-catalyzed oxidation of 2-chloro-4-(methylsulfonyl)toluene to 2-chloro-4-(methylsulfonyl)benzoic acid has been developed with an excellent yield of 84.2% and a purity of 99.7%. The optimized reaction conditions (160 °C, oxygen pressure 1.5 MPa, HNO_3 concentration 25 wt%, HNO_3: substrate 0.5:1) use 1.0 mol% CuI as catalyst. The dosage of HNO_3 in the new process is only 25% of the stoichiometric amount and 12.5% of the amount of the traditional process. The NO_x emission is 5% amount of the traditional process. The oxidation of several additional toluene derivatives with comparable yields demonstrates the generality to these reaction conditions.

Keywords HNO_3-catalyzed oxidation · NO_x recycling · Benzylic oxidation · 2-Chloro-4-(methylsulfonyl)benzoic acid

Introduction

3-[2-Chloro-4-(methylsulfonyl)benzoyl]bicyclo[3.2.1]octane-2,4-dione is a new type of triketone herbicide (Komatsubara et al. 1996) with high economic value and good market prospects. Therefore, the development of a practical synthesis of its intermediate, 2-chloro-4-(methylsulfonyl)benzoic acid, was needed. Its literature synthesis (Brown 1995; Siddall et al. 2001; Adachi et al. 2007) is environmentally unfriendly with low atom economy. Hence, our objective was a green, process-scale synthesis (Figs. 1, 2).

The preparation of 2-chloro-4-(methylsulfonyl)benzoic acid from 2-chloro-4-(methylsulfonyl)toluene is a typical example of the benzylic oxidation of a substituted toluene—a reaction widely used in the synthesis of pesticides, pharmaceuticals, spices, dyes and other fields. This oxidation may be performed using chemical oxidation, electrolytic oxidation, or microbial biochemical oxidation. Chemical reagent oxidation (Brown et al. 1994; Li et al. 2012; Wu et al. 2008; Fukunaga et al. 1995) is difficult to control, and typically generates the reduced oxidation agent as waste liquid, a form that is difficult to treat. Stoichiometric oxidation by HNO_3 (Di Somma et al. 2017) does not require the presence of nitrite ions or HNO_2 in solution, and is a simple and feasible reaction, but needs high temperature, large quantities of HNO_3, and produces too much NO_x pollution. The $Co(OAc)_2/NaBr/AcOH$ catalytic system (Roehrscheid 1992; Roehrscheid 1990; Yan et al. 2011) uses cheap air as an oxidant. However, the oxidation ability of oxygen is limited, resulting in low conversion of the reagent unless high concentrations are used. However, it is difficult to regenerate the catalyst and to suppress side reactions. Electrolytic oxidation (Kreh et al. 1987, 1989) and microbial oxidation (Ishii and Sakaguchi 2006; Sheldon and Arends 2006; Paul et al. 2005; Cull et al. 2000) of aromatic hydrocarbons have the advantages of high selectivity, little environmental pollution, and simple operation. But electrolytic oxidation requires the development of electrolytic equipment and uses large power consumption. For microbial oxidation, finding a specific and robust (not easily inactivated) catalytic enzyme is extremely hard. Both of above methods are not mature enough to meet industrial requirements.

In this paper, we report the preparation of 2-chloro-4-(methylsulfonyl)benzoic acid by an improved HNO_3-

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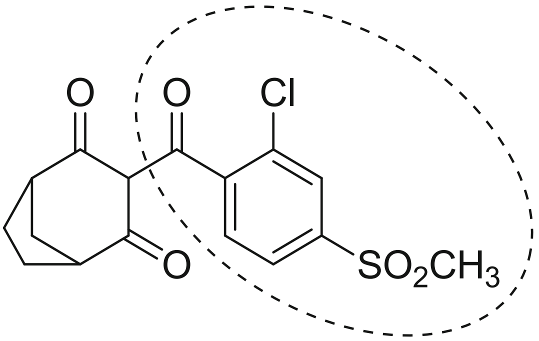


Fig. 1 The structure of the triketone herbicide

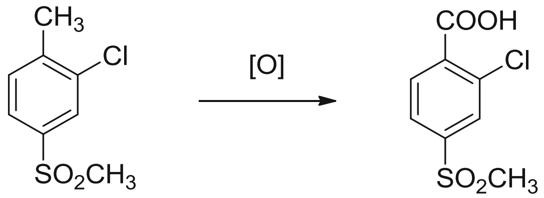


Fig. 2 Oxidation of 2-chloro-4(methylsulfonyl)toluene to 2-chloro-4-(methylsulfonyl)benzoic acid

catalyzed oxidation method (Chen et al. 2015), that is fundamentally different from the traditional HNO_3 oxidation method. HNO_3/CuI is used as catalysts in a pressurized oxygen atmosphere, realizing the transfer of oxygen and regeneration of NO_x. The HNO_3 initiates a chain oxidation of the benzyl alcohol, mediated by (H)NO_x species, and O_2 as the terminal oxidant. The experimental operation is simple, and the dosage of HNO_3 and NO_x emission is reduced compared with the traditional process. The generality of the reaction with respect to different substituents was proven, and this generality promotes the possible application of this CuI/HNO_3-catalyzed for application to other aromatic hydrocarbon oxidations (Fig. 3).

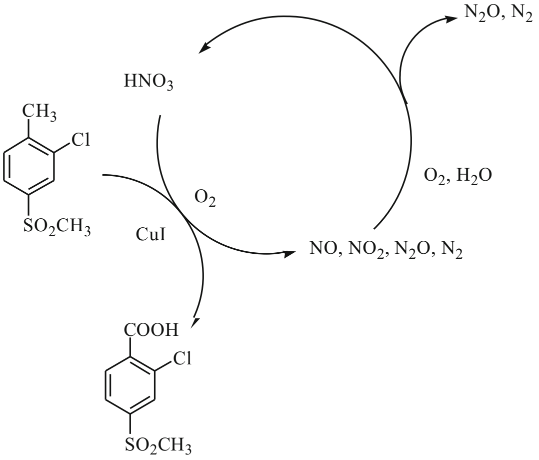


Fig. 3 Reuse of the NO_x to synthesize 2-chloro-4-(methylsulfonyl)benzoic acid

Results and discussion

The route leading to 2-chloro-4-(methylsulfonyl)benzoic acid is illustrated (Fig. 4).

To improve the product yield and to optimize the reaction conditions, the one-variable method was used to analyze process parameters. In the reaction, HNO_3 decomposes and produces reactive oxygen species. Because temperature has great influence on this decomposition and the ensuing oxidation reactions, the selection of the correct reaction temperature is critical to the reaction optimization. The conversion of NO and O_2 to NO_2 occurs in the gas phase, and the reaction pressure also reflects the amount of oxygen in the system, so identifying the best reaction pressure is also important. Lastly, reaction time greatly influences the selectivity of the reaction and the yield of the product. We identified a significant improvement in the reaction with different concentrations of HNO_3 at a temperature of 160 °C, an oxygen pressure of 1.5 MPa, and a reaction time of 4 h (Tables 1, 2; Fig. 5).

It is important to note that the reduction product of concentrated HNO_3 is mainly NO_2, while the reduction product of less concentrated HNO_3 is mainly NO, and the reduction products of dilute HNO_3 are mainly N_2O, N_2, and ammonium nitrate. The concentration of HNO_3 determines whether the reduction product can combine with oxygen to produce HNO_3 and recycle. Using the above optimal conditions, the best concentration of HNO_3 for the reaction was explored. In an initial experiment, 5 wt% HNO_3 gave a yield of the benzoic acid that was only 38.5%. At this low concentration of HNO_3, the

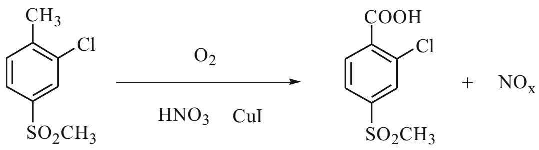


Fig. 4 Oxidation of 2-chloro-4(methylsulfonyl)toluene to 2-chloro-4-(methylsulfonyl)benzoic acid

Table 1 The effect of reaction temperature on the oxidation reactions

Entry	Temperature (°C)	Conversion rate (%)	Selectivity (%)	Yield (%)
1	100	0	0	0
2	120	23.5	90.3	21.2
3	140	69.8	88.3	61.6
4	150	93.5	87.5	81.8
5	160	98.7	85.3	84.2
6	170	99.2	80.2	79.6
7	180	99.6	75.3	75.0

Table 2 The effect of pressure on the oxidation reactions

Entry	Oxygen pressure (MPa)	Conversion rate (%)	Selectivity (%)	Yield (%)
1	0	17.9	86.3	15.4
2	0.5	47.8	85.9	41.1
3	1.0	77.9	87.3	68.0
4	1.5	98.7	85.3	84.2
5	2.0	99.0	85.5	84.6
6	2.5	99.7	85.8	85.5

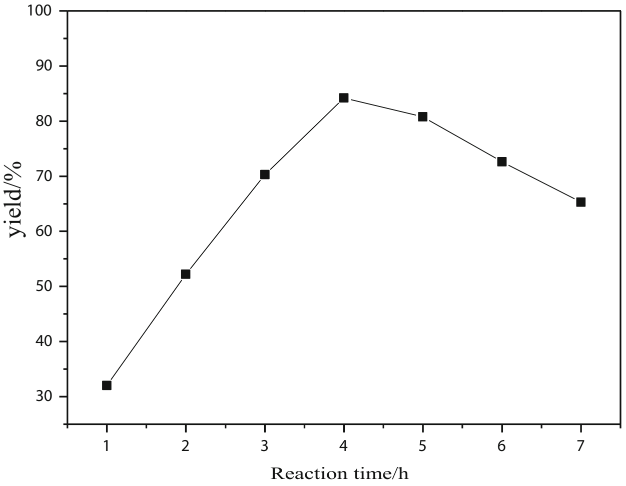


Fig. 5 The effect of reaction time on the oxidation reactions

Table 3 Different concentration of HNO_3 in the oxidation reactions

Entry	HNO_3 concentration (wt%)	Conversion rate (%)	Yield (%)
1	65	99.4	84.0
2	40	99.0	83.8
3	25	98.7	84.2
4	20	96.2	80.3
5	15	87.2	73.7
6	10	78.7	66.1
7	5	45.3	38.5

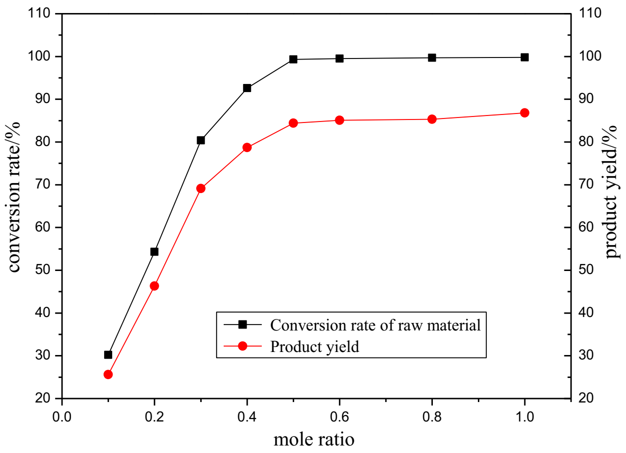


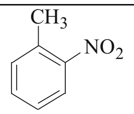
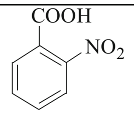
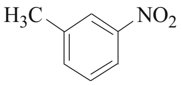
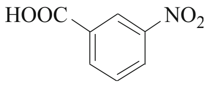
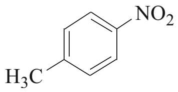
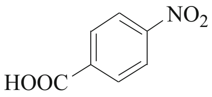
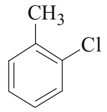
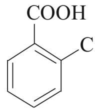
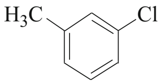
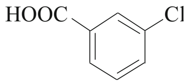
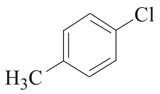
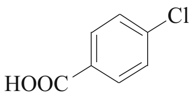
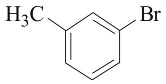
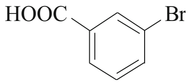
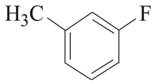
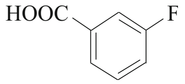
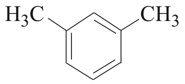
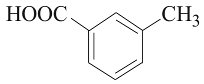
Fig. 6 The effects of quantity of HNO_3 on the oxidation reaction

stoichiometry of HNO_3 is just 0.5 times of the toluene starting material, and the primary reduction products (N_2O and N_2) are unreactive with oxygen. Hence, we explored increased HNO_3 concentrations to allow a better combination of NO_x, oxygen, and water so as to recycle the HNO_3. The results for these different concentrations are given in Table 3.

Concentrations of HNO_3 lower than 25 wt% are not sufficient to oxidize the toluene completely, because HNO_3 recycling is inefficient during the reaction. When the concentration of HNO_3 is higher than 25 wt%, the corrosion effect on the equipment is not acceptable. Table 3 reveals that 25 wt% HNO_3 gives both an excellent conversion rate and an excellent product yield. The amount of HNO_3 directly relates to economic performance and NO_x emission. At atmospheric O_2 pressure, the molar amount of HNO_3 required is four times that of the toluene. As a result, the treatment of the tail gas is necessary to prevent pollution of the environment. For this reason, reducing the dosage of HNO_3 has great practical significance. Figure 6 shows that the best molar ratio of HNO_3 to raw material is 0.5–0.6. The conversion rate and yield are not improved when the molar ratio exceeds 0.6 because the amount of HNO_3 in the system and the amount of recycled HNO_3 are exactly enough at the 0.5–0.6 molar ratio for successful oxidation.

These optimal oxidation conditions—25 wt% (concentration), 0.5 equivalent (dosage) HNO_3, 160 °C, 1.5 MPa O_2 pressure, 1.0 mol% CuI—were examined for nine electronically and sterically varied toluenes (Table 4). The conversion rate of the toluene and the product yield are higher when the substituents are in the *para*-position compared to the *ortho*-position, presumably for steric reasons. In addition, HNO_3 oxidation is a free radical reaction. If the intermediate free radicals are stable, the reaction will be fast and will have good selectivity. Electron-withdrawing groups (–NO_2 or –Cl) have a conjugation effect on the *para*-methyl groups, which stabilize the *para*-methyl radical making the reaction rate fast and the selectivity good. Electron-withdrawing groups at the meta-positions of toluene are more reactive than the ones with electron-donating groups (Table 4, entries 2, 5, 7–9). With decreasing electron-withdrawing ability, the reaction time is shortened, the conversion rate increases, and the yield increases. The one exception (with the poorest yield) is meta-xylene. Its two methyl groups oxidize simultaneously

Table 4 The results for different substituted toluenes

Entry	Substrate	Product	Conversion rate (%)	Yield (%)
1			90.3	80.3
2			95.7	83.2
3			98.6	89.7
4			94.5	83.6
5			97.2	86.5
6			99.8	93.2
7			98.9	89.0
8			95.9	84.7
9			100	53.4

and meta-phthalic acid is a co-product (although the conversion rate is 100%).

The advantages of this new HNO_3-catalyzed oxidation of toluenes to the benzoic acids compared with the traditional method are listed in Table 5, using 2-chloro-4-(methylsulfonyl)benzoic acid as the example. Notably, for new process the dosage of HNO_3, the NO_x emission, and reaction temperature are all decreased. The operation is simpler, the yield is higher, and the system is more stable compared with the traditional process (Li et al. 2012).

Table 5 Comparision of new and traditional processes

Comparison	New process	Traditional process
Dosage of HNO_3	0.5 equivalent	4.0 equivalent
NO_x emission (mol%)	0.2	3.8
Adding method	All reagents combined	Drop
Operation	Simple	Complex
Pressure	1.5 MPa	Atmospheric pressure
Reaction temperature	160 °C	180–200 °C
Stability	Stable	not easy to control
Product yield (%)	84.2	75.6

Experimental section

All the organic reagents were commercial products from Aladdin® with the highest purity available (>98%) and were used without further purification. HNO_3, CuI, NaOH and HCl were commercial products from Sinopharm Chemical Reagent Co.,Ltd with a purity of over 99% and were used as received.

2-Chloro-4-(methylsulfonyl)toluene (0.100 mol, 20.50 g), CuI (0.001 mol, 0.19 g) and 25 wt% HNO_3 (12.60 g) were added in sequence to a 100 mL high pressure reaction kettle equipped with stirrer and a temperature measuring device. Oxygen gas filled the kettle until the pressure was 1.5 MPa. The reaction solution was heated to 160 °C slowly (approximately 0.7 h). The autoclave pressure was raised to 2.5 MPa. The reaction was continued for 4 h with stirring at keeping 160 °C (thermostated). At the conclusion of the reaction the pressure declined to 0.8 MPa and was stable (9 mol% NO_2 and 5 mol% NO, gaseous species concentration determined by the concentration of NO_2^- and NO_3^- after passing the gas through NaOH solution). Thin layer chromatography (TLC) was used to determine reaction conversions in some instances. After the reaction was finished, a 25 wt% NaOH solution (0.200 mol NaOH) was added into the reaction solution and stirring was continued. After reduced pressure filtering, 36 wt% hydrochloric acid was used to adjust the pH of the filtrate to pH 2. The resulting precipitate was collected by filtration. This precipitate was added to MeOH (110 mL) containing 3.00 g of activated carbon. The mixture was heated gently to reflux temperature (60 °C). The precipitate dissolved completely. Stirring was continued for 1 h. The mixture was filtered, and allowed to cool at 10 °C. After 8 h at −5 °C the reaction was filtered. The solid precipitate was dried at 80 °C for 5 h to give 19.70 g (0.084 mol) of the product as white crystals. The yield was 84.2% and the product purity was 99.7%.

Product analysis

TLC was carried out using commercial aluminum-backed plates of silica gel 60 F-254, visualized under 254 and 365 nm radiation. The product and reactant were analyzed through expanding agent (methanol: chloroform = 1:1, plus two drops of acetic acid). Standard sample of 2-chloro-4-(methylsulfonyl)benzoic acid ($R_f = 0.4$), reactant ($R_f = 0.6$) and product ($R_f = 0.4$). Melting points were determined in open capillaries using an Electrothermal 9100 without further corrections. The melting point of the product is 193.8–194.3 °C, consistent with the literature value.

^1H NMR and ^{13}C NMR spectra were recorded using Bruker DRX-400 spectrometer. For 2-chloro-4-(methylsulfonyl)benzoic acid, ^1H NMR (400 MHz, d_6-Acetone) δ 8.10 (t, $J = 6.4$ Hz, 1H), 8.06 (d, $J = 1.6$ Hz, 1H), 8.01 (dd, $J = 8.1$, 1.7 Hz, 1H), 3.26 (s, 3H); ^{13}C NMR (101 MHz, d_6-Acetone) δ 166.79, 146.52, 137.50, 135.07, 133.66, 131.17, 127.64, 44.88.

2-Nitrobenzoic acid: m.p. 145–146 °C; ^1H-NMR (400 MHz, d_6-DMSO) δ 7.97 (d, $J = 8.0$ Hz, 1H), 7.85 (d, $J = 6.8$ Hz, 1H), 7.74–7.81 (2H, m); ^{13}C-NMR (101 MHz, d_6-DMSO) δ 165.9, 148.4, 133.1, 132.4, 129.9, 127.3 123.7.

3-Nitrobenzoic acid: m.p. 139–140 °C; ^1H-NMR (400 MHz, d_6-DMSO) δ 8.61 (s, 1H), 8.46 (d, $J = 8.0$ Hz, 1H), 8.34 (d, $J = 8.0$ Hz, 1H), 7.80 (t, $J = 8.0$ Hz, 1H); ^{13}C-NMR (101 MHz, d_6-DMSO) δ 165.9, 148.4, 133.1, 132.4, 129.9, 127.3, 123.7.

4-Nitrobenzoic acid: m.p. 238–240 °C; ^1H NMR (400 MHz, d_6-DMSO) δ 8.12 (d, $J = 8.4$ Hz, 2H), 8.27 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (101 MHz, d_6-DMSO) δ 123.7, 130.7, 136.4, 150.0, 165.8.

2-Chlorobenzoic acid: m.p. 141 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 9.26 (s, br, 1H), 8.09–7.84 (m, 1H), 7.47–7.35 (m, 2H), 7.29 (tt, $J = 6.3$, 4.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.90, 133.74, 132.57, 131.46, 130.48, 127.42, 125.68.

3-Chlorobenzoic acid: m.p. 137–138 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 13.29 (s, br, 1H), 8.02 (t, $J = 1.8$ Hz, 1H), 7.93 (dd, $J = 7.8$, 1.1 Hz, 1H), 7.52 (ddd, $J = 8.0$, 2.0, 1.0 Hz, 1H), 7.35 (t, $J = 7.9$ Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.98, 133.69, 132.88, 129.96, 129.24, 128.82, 127.30.

4-Chlorobenzoic acid: m.p. 250 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 12.01 (s, br, 1H), 8.10–7.83 (m, 1H), 7.39 (d, $J = 6.7$ Hz, 1H), 7.19 (d, $J = 2.1$ Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.5, 137.8, 131.3, 129.6, 128.7.

3-Bromobenzoic acid: m.p. 155–156 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, $J = 1.3$ Hz, 1H), 7.98 (d, $J = 7.8$ Hz, 1H), 7.67 (d, $J = 7.9$ Hz, 1H), 7.29 (td, $J = 7.9$, 2.0 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 169.84, 135.79, 132.17, 130.14, 129.06, 127.74, 121.56.

3-Fluorobenzoic acid: m.p. 122–123 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (s, 1H), 7.45 (d, $J = 5.6$ Hz, 1H), 7.80 (d, $J = 8.4$ Hz, 1H), 7.91 (d, $J = 6.8$ Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 116.9, 117.1, 120.8, 121.0, 125.9, 130.1, 130.2, 131.5, 131.4, 161.3, 163.7, 171.2.

3-Methylbenzoic acid: m.p. 112–114 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 10.52 (s, br, 1H), 7.85 (d, $J = 7.8$ Hz, 2H), 7.34 (d, $J = 7.5$ Hz, 1H), 7.28 (t, $J = 7.6$ Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.61, 137.27, 133.57, 129.68, 128.23, 127.35, 126.35, 20.22.

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