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Synthesis of 2-Nitro-4-methylsulfonylbenzoic Acid

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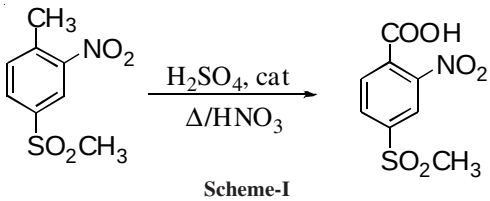
2-Nitro-4-methylsulfonylbenzoic acid was synthesized by the oxidation of 2-nitro-4-methylsulfonyl toluene with hydrogen peroxide in the presence of CuO/Al_2O_3, which was first used in strong acid system. Furthermore, the process of the reaction was thoroughly investigated by varying reactant molar ratio, reaction temperature and the amount of catalyst to obtain the optimum process. Meanwhile, unreacted 2-nitro-4-methylsulfonyl toluene can be recycled after simple treatment. The yield can reach 78.3 %. The method demonstrated the following advantages. Firstly, the oxidant dosage of sulfuric acid and hydrogen peroxide will be reduced greatly. Secondly, unreacted 2-nitro-4-methylsulfonyl toluene can be recycled. Thirdly, this process had good performance on safety. It will be a high-efficiency, energy-saving and environment-friendly technology to produce 2-nitro-4-methylsulfonylbenzoic acid.

Keywords: 2-Nitro-4-methylsulfonylbenzoic acid, CuO/Al_2O_3 catalyst, Hydrogen peroxide, Yield.

INTRODUCTION

2-Nitro-4-methylsulfonylbenzoic acid[1-6] (NMSBA) is an important organic intermediate widely applied in the fields of dye, medicines and pesticides. Meanwhile, it also exhibited some biological characteristics[7]. As some pharmaceutical products and pesticide Mesotrione developed successfully. The market demand of 2-nitro-4-methylsulfonylbenzoic acid had increased dramatically. As early as in the last century 60s, the synthetic method of 2-nitro-4-methylsulfonylbenzoic acid had been reported firstly. Until now, there have been many synthetic methods[8-23] reported in the literatures among which have drawn much attention because of the oxidation of 2-nitro-4-methylsulfonyl toluene (NMST) with concentrated nitric acid.

However, there were some disadvantages included more violent phenomena, lower selectivity and more side reaction if using high concentration of nitric acid as the oxidant. Besides, a lot of NO_x will be generated, which will make the pressure of reaction system increased and caused air pollution easily. In contrast, the process using dilute nitric acid as the oxidant can decrease the side reaction while the dilute nitric acid will make serious corrosion for equipment. In addition, there was potential risk of explosion due to the instability of nitro-compound and high reaction temperature. The production process of 2-nitro-4-methylsulfonylbenzoic acid by making use of nitric acid as the oxidant was shown in **Scheme-I**[16,17].

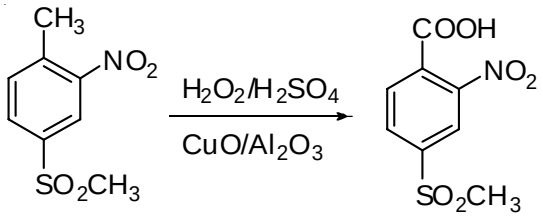


Scheme-I

According to the literature[24-26], some researchers have studied the oxidation system including making use of hydrogen peroxide as the oxidant and inorganic metal or metal salt as the catalyst. Compared with the present industrial technology, this process demonstrated moderate reaction conditions and safety operations. At the same time, the whole process will not generate unstable polynitro compounds and poisonous gas nitrogen oxides. Because of this, the new process may be a clean oxidation route.

However, only using hydrogen peroxide as the oxidant, the actual dosage of hydrogen peroxide will be 17 times as much as the theoretical molar ratio. The highest yield can reach only 40 %, even though the addition of some catalyst such as copper powder, ferrous chloride, sodium tungstate, cobaltous sulfate, cuprous chloride, copper chloride and sodium molybdate. Moreover, large amount of sulfuric acid made it difficult to separate out product and to deal with large quantity of waste acid, which have greatly affected the industrial production of 2-nitro-4-methylsulfonylbenzoic acid.

Therefore, to make this method more efficient, we mainly investigated the synthesis of 2-nitro-4-methylsulfonylbenzoic acid by the oxidation of 2-nitro-4-methylsulfonyl toluene with hydrogen peroxide in the presence of CuO/Al_2O_3. The synthetic route was shown in **Scheme-II**. It was aimed at optimizing the production process including lowering reaction temperature, reducing the potential danger and decreasing the dosage of sulfuric acid and hydrogen peroxide to increase the yield and reduce economic cost.



Scheme-II

EXPERIMENTAL

High performance liquid chromatography HPLC Agilent 1100. Nuclear magnetic resonance instrument Mercury 300 MHz ($CDCl_3$ as solvent, TMS as internal standard). Copper, aluminum, iron are commercially available CP. Concentrated sulfuric acid AR. 45 % hydrogen peroxide, 2-nitro-4-methyl sulfonyl toluene, ethyl acetate were industrial products.

Synthesis: 2-Nitro-4-methyl-sulfonyl toluene (NMST) 8.8 g (0.04 mol) was added to the solution of concentrated H_2SO_4 80 g (0.80 mol) in a 500 mL flask at 60 °C. Then the catalyst CuO/Al_2O_3 was added after stirring for 5-8 min. After another 5-8 min, 45 % H_2O_2 22.2 g (0.28 mol) was dropped slowly. Then the mixture was heated to 60~65 °C and stirred for another 3-4 h. After cooling the solution to the ambient temperature, the same weigh of water as the concentrated H_2SO_4 was added slowly. The light yellow crystal was precipitated, which was the product 2-nitro-4-methylsulfonyl benzoic acid after filtering, washing and drying at 60 °C. The yield can reach 73.2 %. ^{1}H NMR (DMSO, 300 MHz) δ: 8.51 (s, 1H, Ph-a-H), δ: 8.32 (d, J = 8.1 Hz, 1H, Ph-c-H), δ: 8.1 (d, J = 8.1 Hz, 1H, Ph-b-H), δ: 3.34 (s, 3H, SO_2CH_3).

RESULTS AND DISCUSSION

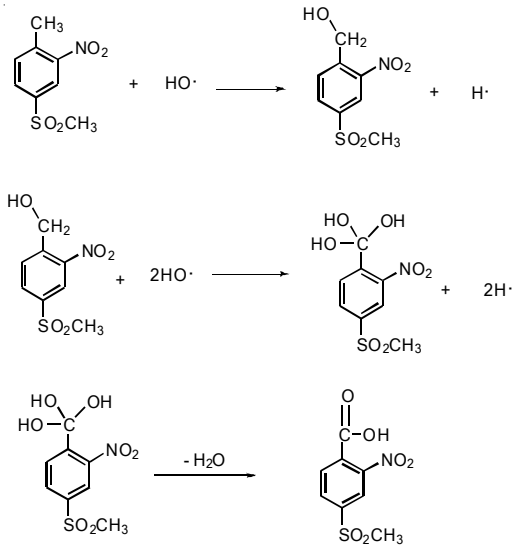
Among the above catalysts, copper powder was the best to catalyze the hydrogen peroxide. However, the yield was only 39.2 % as reported in literature[24].

In order to explore a high-yield and environment-friendly synthetic route, we first discussed the mechanism of the reaction. It was inferred that copper can be oxidized to Cu^{2+}, while only traces of copper was oxidized to Cu^+. The reaction that copper ion catalyze the decomposition of H_2O_2 belongs to a classical Fenton reaction. The reaction mechanism[27-29] was shown as follows.

$$Cu^{2+} + H_2O_2 \longrightarrow Cu^+ + HO_2^{\bullet} + H^+ \quad (1)$$

$$Cu^+ + H_2O_2 \longrightarrow Cu^{2+} + HO^{\bullet} + OH^- \quad (2)$$

$$2H_2O_2 \longrightarrow HO^{\bullet} + HO_2^{\bullet} + H_2O \quad (3)$$



(4)

Specifically speaking, the reaction between Cu^+ and H_2O_2 to form $HO^{\bullet}$ was fast and the reaction 1 was relatively slow, Cu^{2+} reacted slowly with H_2O_2 to form Cu^+. The constant transformation between Cu^+ and Cu^{2+} made chemical reactions proceed smooth. Then $HO^{\bullet}$ generated as the formula (1-3) will convert 2-nitro-4-methylsulfonyl toluene into 2-nitro-4-methylsulfonylbenzoic acid according to the mechnism shown in the formula 4.

In the whole process, copper ion promoted decomposition of H_2O_2 to $HO^{\bullet}$ and increased the efficiency of H_2O_2. In theory, multivalent transition metal ion plays a similar role in catalyzing the decomposition of H_2O_2. Thus, we have first investigated the effect of several transition metals which were similar to copper as the catalyst.

Testing of catalyst: The preliminary reaction conditions were determined in accordance with the literature reported, such as the amount of H_2O_2 *vs.* H_2SO_4, catalyst and reaction temperature. 2-Nitro-4-methylsulfonyl toluene 8.8 g (0.04 mol) was added to the solution of concentrated H_2SO_4 100 g (1.0 mol) in a three-necked flask. Then different catalyst was added after stirring for 5-8 min. After another 5-8 min, 45 % H_2O_2 31.7 g (0.4 mol) was dropped slowly. Then the mixture was heated to 70-75 °C and stirred for another 3-4 h. Post-processing was shown in experimental section.

We selected different catalysts including copper, aluminum, iron, cuprous chloride and zinc chloride to study their catalytic performance. The results showed that the metal copper exhibited the best catalytic effect. However, more products can be precipitated using metal aluminum as the catalyst. In view of the poor catalytic performance of aluminum, we studied the performance of the catalyst with different CuO/Al_2O_3 ratios. It is found that adequate amount of aluminum will impel the oxidation reaction. Therefore, we choose the CuO/Al_2O_3 carrier catalyst to investigate the oxidation of 2-nitro-4-methylsulfonyl toluene to 2-nitro-4-methylsulfonylbenzoic acid by hydrogen peroxide[30].

Optimization of process condition with CuO/Al_2O_3 as catalyst

Effect of different temperature on CuO/Al_2O_3 catalytic performance: 2-Nitro-4-methylsulfonyl toluene 8.8 g (0.04

mol) was added to the solution of concentrated H_2SO_4 100 g (1.0 mol) in a 500 mL flask at different preset temperature. Then the catalyst CuO/Al_2O_3 was added after stirring for 5-8 min. After another 5-8 min, 45 % H_2O_2 31.7 g (0.4 mol) was dropped slowly. Then the mixture was heated to different preset temperature and stirred for another 3-4 h. Post-processing was shown in experimental section. It was discussed the effect of different temperature on the yield of product. The data was shown in Fig. 1. Furthermore, the reaction temperature 50 °C generally means the range of 55-60 °C, similar to the following.

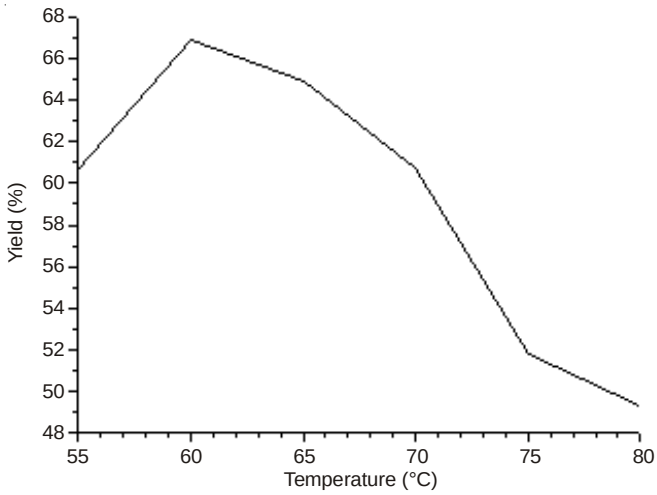


Fig. 1. Effect of the temperature

It can be inferred from Fig. 1 that different temperature had great effect on the reaction yield. When the oxidation reaction happened at a high temperature, some organic compound will be decomposed. And it also promoted the decomposition of hydrogen peroxide, which made the utilization rate of hydrogen peroxide reduce. Besides, high temperature also made the reaction not easy to control and increased the potential risk. Considering yield and safety, the reaction temperature 60 °C was chosen as the most suitable technological condition.

Effect of different amount of H_2O_2 on the yield of product: 2-Nitro-4-methylsulfonyl toluene (NMST) 8.8 g (0.04 mol) was added to the solution of concentrated H_2SO_4 100 g (1.0 mol) in a 500 mL flask at 60 °C. Then the catalyst CuO/Al_2O_3 was added after stirring for 5-8 min. After another 5-8 min, different amount 45 % H_2O_2 was dropped slowly. Then the mixture was heated to 60-65 °C and stirred for another 3-4 h. Post-processing was shown in experimental section. It was discussed the effect of different amount of H_2O_2 on the yield of product. The data was shown in Fig. 2.

It was shown in Fig. 2 that 2-nitro-4-methylsulfonyl toluene had been converted to 2-nitro-4-methylsulfonylbenzoic acid when the molar ratio of 2-nitro-4-methylsulfonyl toluene and hydrogen peroxide reached 1:7. With the amount of hydrogen peroxide added, the yield appeared reverse. Meanwhile, excess hydrogen peroxide can raise the temperature of reaction system, which may result in more side reactions. Thus, the optimal amount of hydrogen peroxide was NMST:H_2O_2 = 1:7 (mol/mol).

Effect of different amount of conc. H_2SO_4 on the yield of product: 2-Nitro-4-methylsulfonyl toluene (NMST) 8.8 g

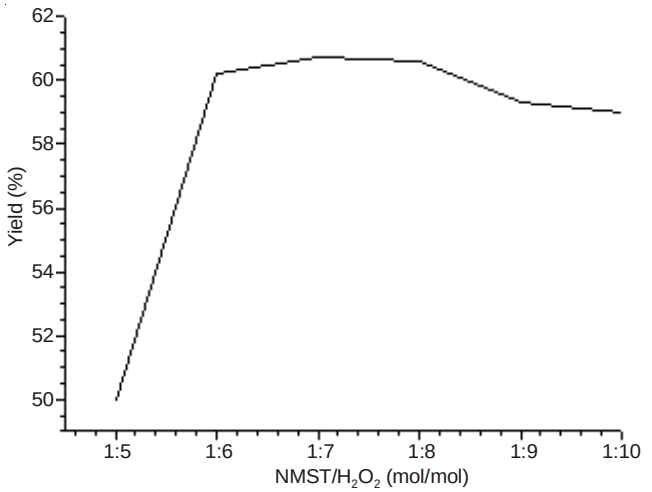


Fig. 2. Effect of the quantity of H_2O_2

(0.04 mol) was added to concentrated H_2SO_4 80 g (0.8 mol) in a 500 mL flask at 60 °C. Then the catalyst CuO/Al_2O_3 was added after stirring for 5-8 min. After another 5-8 min, 45 % H_2O_2 22.2 g (0.28 mol) was dropped slowly. Then the mixture was heated to 60-65 °C and stirred for another 3-4 h. Post-processing was shown in experimental section. It was discussed the effect of different amount of H_2SO_4 on the yield of product. The data was shown in Fig. 3.

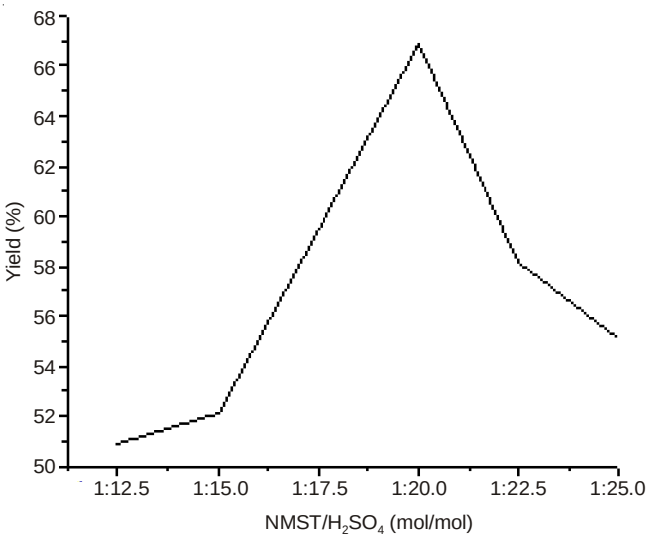


Fig. 3. Effect of the quantity of H_2SO_4

With the amount of concentrated H_2SO_4 increasing, the yield was also increasing accordingly. However, when the amount of concentrated H_2SO_4 reached 80 g (NMST:H_2SO_4 = 1:20 (mol/mol)), the yield reached the peak. It can be explained that too much concentrated H_2SO_4 will make the precipitation of product more difficulty and lower the yield at the same time. Thus the optimal amount of sulfuric acid was NMST:H_2SO_4 = 1:20 (mol/mol).

Effect of different amount of catalyst on the yield of product: 2-Nitro-4-methylsulfonyl toluene (NMST) 8.8 g (0.04 mol) was added to a solution of concentrated H_2SO_4 80 g (0.8 mol) in a 500 mL flask at 60 °C. Then different amount of catalyst was added after stirring for 5-8 min. After another 5-8 min, 45 % H_2O_2 22.2 g (0.28 mol) was dropped

slowly. Then the mixture was heated to 60-65 °C and stirred for another 3-4 h. Post-processing was shown in experimental section. It was discussed the effect of different amount of catalyst on the yield of product. The data was shown in Fig. 4. Furthermore, the amount of catalyst was equal to 8.8 g (0.04 mol) 2-nitro-4-methylsulfonyl toluene.

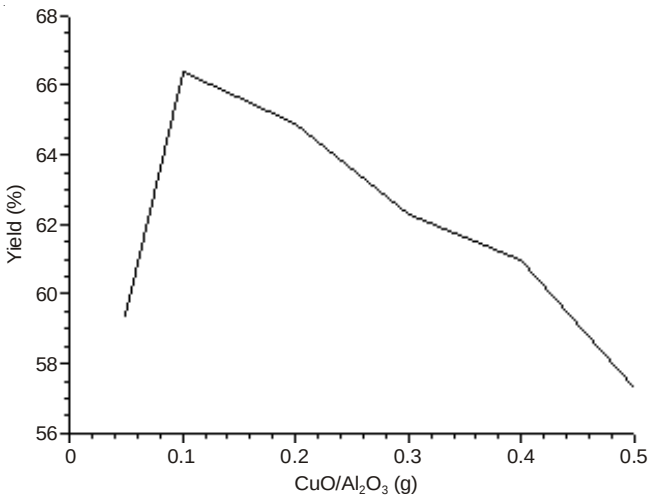


Fig. 4. Effect of the quantity of CuO/Al_2O_3

It can be seen in Fig. 4 that using less catalyst made the reaction more difficulty. However, large quantity of catalyst can enhance the conversion of 2-nitro-4-methylsulfonyl toluene but lower the 2-nitro-4-methylsulfonylbenzoic acid selectivity simultaneously, resulting in a significant reduction in the yield. Finally the optimal amount of catalyst was 0.1 g CuO/Al_2O_3 catalyst per 0.04 mol 2-nitro-4-methylsulfonyl toluene.

Orthogonal experiment: According to the single factor experiments, taking the 2-nitro-4-methylsulfonylbenzoic acid yield as the detective marker, the orthogonal experiments of four factors and four levels was applied to optimize the extraction conditions (Table-1).

TABLE-1
DIFFERENT FACTOR 1EVELS

Factor / Level	Temp. (°C)	NMST:H_2O (mol/mol)	NMST:H_2SO_4 (mol/mol)	CuO/Al_2O_3 (g)
1	55	1:5	1:15.0	0.1
2	60	1:6	1:17.5	0.2
3	65	1:7	1:20.0	0.3
4	70	1:8	1:22.5	0.4

NMST = 2-Nitro-4-methylsulfonyl toluene

The optimum conditions can be concluded from the result of orthogonal experiments (Table-2). The reaction temperature was 65 °C, the molar ratio of reactant was NMST:H_2O_2:H_2SO_4 = 1:7:20 and the amount of the catalyst CuO/Al_2O_3 was 2.5 g per mol 2-nitro-4-methylsulfonyl toluene.

Through signal factor and orthogonal experiments, the optimizing experiments had been carried out and the optimal condition was obtained, as shown in Table-3.

Ultimately, the optimum conditions were obtained based on the result of the optimizing experiments. The reaction temperature was 60-65 °C, the molar ratio of reactant was NMST:H_2O_2:H_2SO_4 = 1:7:20 and the amount of the catalyst CuO/Al_2O_3 was 2.5 g per mol 2-nitro-4-methylsulfonyl toluene. The reaction solution was analyzed by HPLC including 84.6 % 2-nitro-4-methylsulfonylbenzoic acid and 12.3 % 2-nitro-4-methylsulfonyl toluene. There was rarely by-product, which will be helpful for further purification. In addition, the unreacted 2-nitro-4-methylsulfonyl toluene can be recycled easily and reused. The 2-nitro-4-methylsulfonylbenzoic acid yield can reach 78.3 % based on 2-nitro-4-methylsulfonyl toluene.

TABLE-2
RESULTS AND ANALYSES OF ORTHOGONAL EXPERIMENTS

Sources code	Temp. (°C)	NMST: H_2O_2 (%)	NMST: H_2SO_4 (%)	CuO/Al_2O_3 (g)	NMSBA Yield (%)
1	55	1:5	1:15	0.1	36. 0
2	55	1:6	1:17.5	0.2	51. 7
3	55	1:7	1:20	0.3	60.6
4	55	1:8	1:22.5	0.4	58. 2
5	60	1:5	1:17.5	0.3	49. 8
6	60	1:6	1:15	0.4	48. 3
7	60	1:7	1:22.5	0.1	56. 3
8	60	1:8	1:20	0.2	60. 2
9	65	1:5	1:20	0.4	59. 6
10	65	1:6	1:22.5	0.3	59. 8
11	65	1:7	1:15	0.2	47. 5
12	65	1:8	1:17.5	0.1	52. 3
13	70	1:5	1:22.5	0.2	49. 1
14	70	1:6	1:20	0.1	54. 3
15	70	1:7	1:17.5	0.4	58. 4
16	70	1:8	1:15	0.3	36. 6
K1	206.5	195.1	168.4	198.9	
K2	214.6	214.1	214.0	208.48	
K3	219.2	222.8	234.7	206.8	
K4	198.4	207.3	223.4	224.5	
k1	51.62	48.62	42.10	49.72	
k2	53.65	53.52	53.05	52.12	
k3	54.80	55.70	58.68	51.70	
k4	49.60	51.82	55.85	56.12	
R	5.20	7.08	16.58	6.40	

NMST = 2-Nitro-4-methylsulfonyl toluene
NMSBA = 2-Nitro-4-methylsulfonylbenzoic acid

TABLE-3
DATA OF OPTIMIZATION OF EXPERIMENT

Number	Temp. (°C)	NMST:H_2O_2:H_2SO_4 (mol/mol/mol)	CuO/Al_2O_3 (g)	NMSBA Yield (%)
1	55	1:7:20	0.1	60.2
2	60	1:7:20	0.1	66.9
3	65	1:7:20	0.1	63.7

NMST = 2-Nitro-4-methylsulfonyl toluene
NMSBA = 2-Nitro-4-methylsulfonylbenzoic acid

Conclusion

The study first successfully applied CuO/Al_2O_3 to oxidize 2-nitro-4-methylsulfonyl toluene to the corresponding acid by hydrogen peroxide in the strong acid system. The optimum conditions were obtained through a large number of experiments. With CuO/Al_2O_3 as the catalyst, it promoted the oxidation ability of hydrogen peroxide. The amount of hydrogen peroxide decreased to 2.3 times as much as the theoretical molar ratio and reaction temperature reduced from 80-130 to

60-65 °C, which reduced the potential danger. Meanwhile, in the whole process, there was no use of nitric acid, which made a high-purity product without polynitro compounds and no pollution gas generated. According to the optimum process conditions, the final yield can reach 78.3 % based on 2-nitro-4-methylsulfonyl toluene. Therefore, this method will be a high-efficiency, energy-saving and environment-friendly technology to product 2-nitro-4-methylsulfonylbenzoic acid, which may be easy for industrialization.

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