

2,3,4,5-Tetrafluorobenzoic Acid의 합성

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Preparation of 2,3,4,5-Tetrafluorobenzoic Acid

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요약. Fluoroquinolone 항생제의 중요한 중간체인 2,3,4,5-tetrafluorobenzoic acid를 tetrachloride phthalic anhydride에서 출발하여 imidation, fluorination, hydrolysis과 decarboxylation 단계를 거쳐서 합성하였다. Imidation 단계에서는 상전이 촉매를 이용하여 98.2%의 수율로 합성하였으며, fluorination 단계에서는 81.3%, 가수분해 단계에서는 88.6%, 마지막으로 decarboxylation 단계에서는 81.6%의 수율로 합성하였다.

주제어: Tetrafluorobenzoic acid, Tetrachloride phthalic anhydride, Imidation, Fluorination, 가수분해, Decarboxylation

ABSTRACT. 2,3,4,5-Tetrafluorobenzoic acid, an important intermediates of fluoroquinolone antibiotics, was synthesized from tetrachloride phthalic anhydride through imidation, fluorination, hydrolysis and decarboxylation. The effects of phase transfer catalyst on imidation and fluorination reaction and the effects of surfactants on the hydrolysis reaction were studied, respectively. Experimental results showed that the imidation reaction time was greatly reduced in the presence of a phase transfer catalyst, hexadecyltrimethyl, resulting in imidation yield as high as 98.2%. The fluorination yield reached 81.3% when tetrabutylammonium bromide was chosen as a phase transfer catalyst. The hydrolysis reaction time was also decreased by adding hexadecyltrimethyl while increasing the yield to 88.6%. In the post-processing, the sublimation method was used to purify the product, and ideal effect was obtained. In the decarboxylation reaction, tetrafluoride phthalic acid was obtained by decarboxylation in the solvent of tri-n-butyl amine and decarboxylation yield reached 81.6%. Compared with the literature method, the overall reaction time of the improved method decreased from 53 h to 20.5 h and the total yield increased from 47.3% to 57.4%.

Keywords: Tetrafluorobenzoic acid, Tetrachloride phthalic anhydride, Imidization, Fluorination, Hydrolysis

INTRODUCTION

2,3,4,5-Tetrafluorobenzoic acid is an important pharmaceutical intermediate, commonly used in preparation of antibacterial agents of quinolone, such as lomefloxacin, sparfloxacin, fleroxacin, ofloxacin, levofloxacin and rifloxacin etc. which is characterized by broad-spectrum antimicrobial activity, high-effective and low cytotoxicity to human. Quinolone drug is clinically recognized to be a powerful and safe weapon for the treatment of various bacterial infections and has become a blockbuster drug, with annual sales of around 3 billion dollars worldwide. Quinolone drug is synthesized from 2,3,4,5-tetrafluorobenzoic acid, so the development of 2,3,4,5-tetrafluorobenzoic acid has good social

and economic forecast. In the field of medicines for antibiotic therapy, the global market focus is transferring from cephalosporin to fluoroquinolones. Therefore, it is meaningful to study a suitable industrial routine for the synthesis of 2,3,4,5-tetrafluorobenzoic acid.

The synthetic methods of 2,3,4,5-tetrafluorobenzoic acid can be summarized according to the different raw materials. ① 1,2,3,4-tetrachloro-phthalicanhydride,^{1,2,3} ② O-phthalodinitrile,⁴ ③ N-phenyltetrachlorophthalimidine, ④ Otachloro-naphthalene,⁵ ⑤ 1,2,3,4-tetrafluorobenzene,⁶ ⑥ 2,3,4,5-tetrafluoro-benzhydrol etc. therein: ① the process with starting 1,2,3,4-tetrachlorophthalicanhydride and aniline through imidization reaction,^{7,8,9} fluoridization reaction, hydrolysis reaction and decarboxylation reaction is described, this pro-

cess is characterized with plenty raw material source, simple process and mild reaction condition, therefore it is suitable for commercial production. Based on traditional technology, the improved process is researched in the presence of a phase transfer catalyst, the overall reaction time of the improved method decrease from 53 h to 20.5 h and the total yield increase from 47.3% to 57.4%.

EXPERIMENTAL

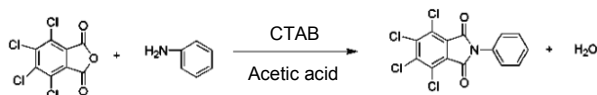
Materials

Potassium fluoride was industrial grade; other reagents were all of AR grade and were obtained from Shanghai Chemical Reagent Co. with purities of 0.995 in mass fraction. Dimethylformamide (DMF), DMSO, TMSO₂ (Sulfolane) were dried and dewatered. Melting point was tested by RD.II digital melting point meter (from Tianjin Instruments Company); Water was determined with DL 18 Karl Fisher titrator; Waters2487 high-performance liquid chromatography was used to HPLC (600 pumps, 600 controllers). IR spectrum was tested by Shimadzu IR2408.

The imidization of Tetrachlorophthalic anhydride

A mixture of 100 mL acetic acid and 25.00 g (0.087 mol) pretreated tetrachlorophthalic anhydride was stirred in a 3-neck round bottom flask equipped with a overhead stirrer, a thermometer, a dropping funnel and a 14-in glass helices-packed column having a variable reflux ratio still-head. 8.55 g (0.092 mol) aniline was added through the dropping funnel at a suitable stirred rate. The reaction temperature was kept at 120 °C and 0.5 g cetyltrimethylammonium bromide was added. External cooling was applied when necessary and the mixture was violently agitated and reacted for 0.5 h then the product was cooled.

The reaction equation was as follows:



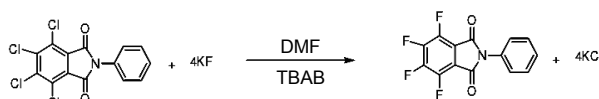
The post-processing method: The mixture was separated and distilled, the obtained product was 30.80 g and the yield was 98.2%, the melting point was 274 - 275 °C, the literature data was 275.3 °C - 275.8 °C.¹⁰

Fluorination¹¹

Tetrachloro-N-phenylphthalimide (15 g, 0.042 moles) was combined in a nitrogen atmosphere with 19.5 g KF (0.34

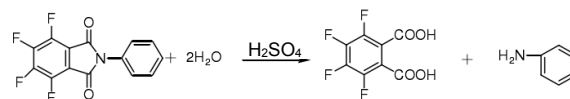
moles; dried 48 hours at 300 °C, 1 mm Hg), 0.3 g tributylhexadecylphosphonium bromide (dried 16 hours at 150 °C, 0.5 mm Hg) and 100 mL dried DMF in a 3-neck round-bottom flask fitted with a cold-water condenser, overhead stirrer and thermometer. The reaction was run under a positive pressure of N₂ at 140 °C for 8 hours. The hot mixture was filtered and the filter cake was washed with acetone. Acetone was flash evaporated from the distillate. The product was separated from the DMF. The solid was filtered, dried and recrystallized, 9.97 g white crystalline solid was obtained and the yield was 81.3%, the melting point was 203 - 204 °C, the literature data was 204 - 205 °C.¹⁰ The product was identified by HPLC and IR.

The reaction equation was as follows:



Hydrolysis

10.0 g N-phenyl phthalimide were put into a 3-neck round-bottom flask, followed by a mixture that 0.05 g hexadecyltrimethyl amino bromide dissolved in 80 mL 80 % sulfuric acid, and this combination was allowed to reflux (110 °C) for 8 hours. The reaction equation was as follows:



The post-processing method: The reaction mixture was adjusted to weakly acidic solution, whose pH was 5, with sodium solution of 20%, and being extracted with 80 mL dichloromethane, then being extracted with dichloromethane (50 mL × 2) for two more times. The combined filtrate was dried by 10 g sodium sulphate anhydrous and filtered to remove sodium sulphate and dichloromethane was evaporated and recycled using a rotary evaporator. 7.15 g white powder was obtained, it's melting point was 145 - 148 °C, literature value was 150 - 151 °C,¹⁰ and the yield was 88.6%.

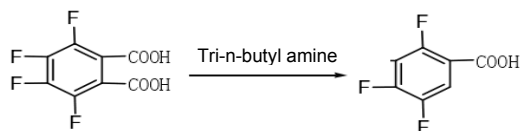
Purifying tetrafluorophthalic acid by sublimation

According to the determination of melting point and HPLC, the purity of the product obtained from above 1.4 was not high enough, thus, the purification of tetrafluoro-

phthalic acid was essential. In this step, sublimation method was used to purify tetrafluorophthalic acid, tetrafluorophthalic acid was increased to 130 - 140 °C and cooled, the white crystalline in high purity with the melting point 150 - 151 °C was obtained.

The synthesis of tetrafluorobenzoic acid

Tri-n-butyl amine 35 mL together with 4 g tetrafluorophthalic acid were added into a 3-neck round-bottom flask, and this combination was allowed to heated to 130 °C and reacted for 4 h and cooled to room temperature. Tetrafluorophthalic acid was treated with Tri-n-butyl amine by decarboxylation to give tetrafluorobenzoic acid. The reaction equation was as follows:



The post-processing method: In view of the price of tri-n-butyl amine was higher, tri-n-butyl amine needed to be recycled. 20% NaOH was added to extract tetrafluorobenzoic acid, then the organic phase was the recycled tri-n-butyl amine and the aqueous phase was treated with concentrated hydrochloric acid, with the mass fraction of about 38%, to adjust the pH to 1, followed by the appearance of gray white precipitate which was obtained by filtering the solution; the solution was extracted with methylene chloride, 10 g anhydrous sodium sulfate was added into the organic phase, gray white solid was given by a rotary evaporator; The gray white solid obtained twice which weighed 2.66 g were the product, melting point was 89 - 91 °C, literature value was 85 - 87 °C,¹⁰ and the yield was 81.6%; In this way, the tri-n-butyl amine was used as solvent replacing of poisonous methylbenzene, therefore the environment pollution can be avoided and the harm to the health of human beings can be decreased.

RESULTS AND DISCUSSION

The effects of phase transfer catalyst on fluorination¹²

As the fluorination of fluoride salt was a solid-liquid reaction, the addition of phase-transfer catalysts could decrease reaction temperature, shorten reaction time and increase yield. Therefore the effects of different phase-transfer catalysts on transformation activity of tetrafluoro products were showed in Table 1. (The reaction temperature was 150 °C and the reaction time was 8 h, then the wavelength

Table 1. The effects of phase transfer catalyst on fluorination

No.	catalysts	Reaction Time (h)	yield (%)
1	TBAB	8	81.3
2	CTAB	8	76.4
3	PEG-6000	8	73.8

The effects of solvent on the fluorination reaction¹³

was determined at 254 nm in the condition that mobile phase anhydrous methanol:water = 4:1 (v:v) and the solvent was DMF, with a flow rate of 1100 mL/min). It could be found from Table 1 that the best catalyst was tetrabutylammonium bromide of quaternary ammonium salts, and the by-product was not found by HPLC.

The Halogen-exchange of tetrachloro-N-phenyl-phthalimide was liquid-solid reaction. Despite the great thermodynamics strength of C-F bond, fluorine was easily replaced by strong nucleophiles, such as hydroxyl, amine etc., because the electronegativity of the element fluorine can make the transition state of reaction steady. Consequently, fluorination should be reacted in anhydrous non-proton polarity solvent to avoid the occurrence of side reaction of fluorine hydrolysis.

The concentration of fluoride in solvents can also influence the rate of fluorination, therefore the solvents must have some solubility to alkali metal salt. The alkali metal salt of fluoride, that was, fluoride, had relatively large solubility in polar solvents,^{14,15} such as tetrahydrofuran, DMF. The increase in solubility of fluoride in polar solvents would increase the reaction rate; hence, non-proton polarity organic solvents with high boiling points were an ideal solvent for the fluorination reaction.

TMSO₂ and DMF were important solvents in industrial fluorination of halogen exchange. But the price of TMSO₂ was 5 times as much as DMF and the boiling point of TMSO₂ was much higher than DMF, so in the consideration of the cost and energy -saving as well as solvent recovery, DMF of lower price was selected to be the solvent in the fluorination in this experiment.

The effects of reaction time on the fluorination reaction

Reaction time was another important factor that influenced the reaction. The reaction was investigated by TLC with the mixture of cyclohexane and ethyl acetate (v:v = 3:1) as developing solvent. The conditions of the reaction were observed and tested by thin-layer chromatography when the reaction time was 3 h, 5 h, 6 h, 7 h, 8 h and 12 h respectively. The effects of different reaction time on fluorination were showed in Table 2.

Table 2. The effect of reaction time on the fluorination reaction

NO.	Reaction Time (h)	Reaction Temperature (°C)	TLC
1	3	140	3 points
2	5	140	3 points
3	6	140	2 points
4	7	140	2 points
5	8	140	1 point
6	12	140	multiple points

Table 3. The effects of reaction temperature on the fluorination reaction

No.	Reaction Temperature (°C)	Reaction Time (h)	Yield (%)
1	120	8	50.3
2	130	8	64.6
3	140	8	80.2
4	150	8	81.5
5	150	12	75.1
6	160	8	73.4
7	170	8	59.8

Table 4. The effects of different surfactants on the hydrolysis

Surfactants	Reaction Time (h)	Yield (%)
CTAB	8	88.6
PEG-6000	8	76.2
without surfactants	8	24.6

Table 5. The effects of different solvents on the synthesis of tetrafluorobenzoic acid

Solvents	Reaction Time (h)	Yield (%)
N,N-dimethylformamide	4	70.5
Dimethyl sulfoxide	4	72.8
Tri-n-butyl amine	4	81.6

It was found from *Table 2* that the appropriate reaction time was 8 h; if the reaction time was shorter, the reaction was incomplete, and some intermediate products of two fluoride and trifluoride were formed. On the contrary, if the reaction time was longer, some side reactions would be occurred.

The effects of reaction temperature on the fluorination reaction

Reaction temperature was very important factor for the reaction. Higher reaction temperature was usually required in nucleophilic fluorination reaction to obtain activation

energy. Reaction temperature influenced greatly not only the yield of end product, but also the degree of fluorination. In order to determine the influences of reaction temperature on the fluorination reaction, reaction temperatures of 120 °C, 130 °C, 140 °C, 150 °C, 160 °C and 170 °C were experimented respectively. The experimental results were showed in *Table 3*.

It was found from *Table 3* that the appropriate reaction temperature was in the range 140 to 150 °C, if the reaction temperature was too high, coking phenomenon was serious in aqueous reaction; otherwise, if the reaction temperature was too low, reaction time would be increased greatly and the reactant did not react completely.

The effects of surfactants on hydrolysis

The effects of different surfactants on the hydrolysis were showed in *Table 4*.

The conventional hydrolysis required 19 h, and the reactants were easy to agglomerate and was not easy to disperse due to their strong hydrophobicity, therefore the addition of surfactant can change the surface of the powder reactants from hydrophobicity to hydrophilicity, which can ensure good dispersion of reactants in the aqueous phase, the reaction time shortened to 8 h. Compare with different surfactants, it was found that cetyl trimethyl ammonium bromide played a very good dispersion effect, the reaction time was 8 h in 88.6% yield. Surfactants with high molecular weight (such as PEG-6000) had a little bad dispersing effect, this may be due to the bridge and flocculation of the large molecules of PEG-6000 between particles. If without surfactant, the yield could only reach 24.6%

The effects of sublimation on the purity of tetrafluorophthalic acid

The high pure white tetrafluorophthalic acid was obtained by sublimation. The melting point was 150 - 151 °C.

The effects of different solvents on the synthesis of tetrafluorobenzoic acid

The effects of N,N-dimethyl formamide, dimethyl sulfoxide, and tributylamine acid on the synthesis of tetrafluorobenzoic acid were studied and the experimental results were showed in *Table 5*:

The yield of tri-n-butyl amine as solvent was 81.6% in *Table 5*, tri-n-butyl amine played three roles in the reaction: (1) the alkaline structure of tri-n-butyl amine can react with hydrogen of the carboxyl group to prompt the decarboxylation reaction; (2) the alkaline structure of tri-n-butyl amine can combine with generated carbon dioxide and promote the

reaction movement towards positive reaction direction; (3) as solvent, tri-n-butyl amine, in the boiling point range 210 to 215 °C, can meet the temperature requirement of decarboxylation reaction in the synthesis of tetrafluorophthalic acid.

CONCLUSION

2,3,4,5-Tetrafluorobenzoic acid was synthesized from 1,2,3,4-tetrachlorophthalic anhydride and aniline through imidization, fluorination, hydrolysis and decarboxylation with tetrabutylammonium bromide as phase transfer catalyst. The experimental results showed that:

(1) In the imidation reaction, N-phenyl-Tetrachloro-phthalimide was synthesized from tetrachloro-phthalic anhydride and aniline as raw materials, the proportion of which was 1.1:1, using acetic acid as solvent and hexadecyltrimethyl ammonium bromide as catalyst, reflux for 0.5 h and the 98.2% yield can be obtained;

(2) In the fluorination reaction, N-phenyl phthalimide was synthesized from N-phenyl-Tetrachloro-phthalimide and potassium fluoride as the raw materials, the ratio of N-phenyl-Tetrachloro-phthalimide to potassium fluoride was 8:1, potassium fluoride as fluoride and DMF as solvent, tetrabutylammonium bromide as catalyst, reaction for 8 h. N-phenyl phthalimide was obtained in 81.3% yield.

(3) In the hydrolysis reaction. Tetrafluorophthalic acid was synthesized from N-phenyl tetrafluoride phthalimide as the raw material, using 80% of sulfuric acid as the solvent, reaction for 8 h at 110 °C, with a yield of 88.6%. In the presence of CTAB, hydrolysis reaction time decreased obviously from 40 h to 8 h and the concentration of the acid increased from 50% to 80%; ether was replaced by dichloromethane in the product treatment; tetrafluorophthalic acid was purified by sublimation;

(4) In the decarboxylation reaction, tetrafluorobenzoic acid was prepared from tetrafluorophthalic acid as raw materials, with tri-n-butyl amine as solvent kept at 130 °C for 4 h and the yield reached 81.6%. An improved method was provided with the tri-n-butyl amine as solvent replacing of

poisonous methylbenzene, and the tri-n-butyl amine can be recycled. Compared with the literature method, the overall reaction time of the improved method decreased from 53 h to 20.5 h and the total yield increased from 47.3% to 57.4%;

(5) The addition of phase transfer catalyst can accelerate the reaction and the amounts of catalyst is 4% (based on the mass of N-phenyl-Tetrachloro-phthalimide);

(6) Potassium fluoride need to be pretreated before reaction, the fineness and water content of potassium fluoride directly influenced the yield of fluorination;

(7) Considering the effect of the reaction temperature of 140 - 150 °C and the recovery of the solvent *etc.*, it was economical and feasible with DMF as the solvent.

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