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Abstract. Tetrachloride hydrochloride is a local anesthetic with long-acting ester, and it is usually present in the form of a hydrochloride salt. Firsleb first synthesized the tetracaine by experiment in 1928, which is one of the recognized clinical potent anesthetics. This medicine has the advantages of stable physical and chemical properties, the rapid role and long maintenance. Tetracaine is also used for ophthalmic surface anesthesia as one of the main local anesthetic just like conduction block anesthesia, mucosal surface anesthesia and epidural anesthesia. So far, the research mainly engaged in its clinical application research, and the research strength is relatively small in the field of synthetic technology. The general cost of the existing production process is high, and the yield is low. In addition, the reaction time is long and the reaction conditions are harsh. In this paper, a new synthetic method was proposed for the synthesis of tetracaine hydrochloride. The reaction route has the advantages of few steps, high yield, short reaction time and mild reaction conditions. The cheap p-nitrobenzoic acid was selected as raw material. By esterification with ethanol and reaction with n-butyraldehyde (the reaction process includes nitro reduction, aldol condensation and hydrogenation reduction), the intermediate was transesterified with dimethylaminoethanol under basic conditions. Finally, the PH value was adjusted in the ethanol solvent. After experiencing 4 steps reaction, the crude tetracaine hydrochloride was obtained.

1. Introduction

Tetracaine hydrochloride is also known as ropivacaine hydrochloride, pantocaine, pantocaine and four ropivacaine hydrochloride. The molecular formula is $C_{15}H_{25}ClN_2O_2$, and the molecular weight is 300.82. The melting point is 147-150 ℃. Its English name is tetracaine hydrochloride CAS NO: 136-47-0. It is easily soluble in water and ethanol, but insoluble in ether, benzene. Tetracaine hydrochloride is a local anesthetic with long-acting ester. In addition, procaine is widely used in clinical, but because of its poor permeability and poor narcotic performance, a small tetracaine was found in 1930 found. Its fat solubility is 100 times than that of procaine, and its effectiveness and maintenance time also correspondingly increased. Compared to procaine, it has high performance on fat-soluble and anesthetic performance, and the anesthesia time is longer. Commonly, the tetracaine with 2% concentration is used for surface anesthesia, and 4%-5% ointment is formulated with an anhydrous machine to apply for skin surface anesthesia. In asdition, it is also used for the tracheal catheter surface to reduce intraoperative airway irritation. Tetracaine hydrochloride can be used for topical anesthesia, and 0.05%-0.1% tetracaine hydrochloride can provide long-term and good effect of surface anesthesia. Meanwhile,

tetracaine hydrochloride is still widely used in ophthalmic surface anesthesia, which has a long time for surface anesthesia and sensory resistance.

2. Experiment part

2.1. Experimental reagents and instruments

The required reagents for the synthesis process of tetracaine hydrochloride are shown in Table 1 and the required equipment for the synthesis process of tetracaine hydrochloride is shown in Table 2:

Table 1. Reagents of experiment

Reagent name	Purity	Manufacturer
Vitriol (98%)	AR	Yantai Sanhe Chemical Reagent Co., Ltd
Muriatic acid (36%)	AR	Yantai Sanhe Chemical Reagent Co., Ltd
zinc powder	Industrial grade	Tianjin Huirui Chemical Technology Co., Ltd
glacial acetic acid	AR	Tianjin Bodi Chemical Co., Ltd
N-butyl aldehyde	AR	Tianjin Guangcheng Chemical Reagent Co., Ltd
p-nitrobenzoic acid	AR	Shanghai Puzhen Biological Technology Co., Ltd

Table 2. Experiment equipment

Equipment	Type	Manufacturer
Rotary evaporator	RE-52AA	Shanghai Yarong Biochemical Equipment Factory
Constant temperature heating magnetic stirring bar	GS-2	Gongyi Instrument Co., Ltd.
Thermostatic water bath	ZXYY-0.5L	Zhengzhou Yingyu Instrument Co., Ltd.
Magnetic stirring bar	84-3	Gongyi Yingyu Instrument Factory
Circulating water vacuum pump	SHZ-D	Gongyi Yingyu Instrument Co., Ltd.
Electronic balance	JA2003N	Shanghai Precision Science Instrument Co., Ltd
Vacuum drying oven	DZF-6020	Shanghai Kesheng Instrument Co., Ltd
Micro melting point apparatus	SGW-4	Shanghai Electric Optical Instrument Co., Ltd
Nuclear magnetic resonance	BRUKER AVANCE500MH$_Z$	Germany - Switzerland Brooke Spectrum Instrument Company

2.2. Experimental steps

2.2.1. Synthesis of ethyl ethyl 4-nitrobenzoate In a 500 mL four-necked flask equipped with a stirrer, thermometer, spherical condenser and constant pressure dropping funnel, 83.5g (0.5 mol) p-nitrobenzoic acid and 115g (2.5 mol) anhydrous ethanol were added. The solution was stirred and mixed evenly, and then 6.8 g (0.05 mol) potassium bicarbonate was dropped. After finishing the adding process, the

temperature was raised to about 80℃ to re-flux. After 3h of the reflux reaction, the mixture solution was cooled to room temperature. 8% sodium carbonate solution was added the reaction solution to adjust the pH value to the range of 7-8, while the water is added to wash. The solution was placed at 0 to 5℃ for low temperature precipitation. Meanwhile, the filtration and washing carried out three times. 93.9g white crystalline solid was obtained after drying. The yield was 93.6%. The nuclear magnetic resonance spectroscopy of the target product was shown in Fig. 1.

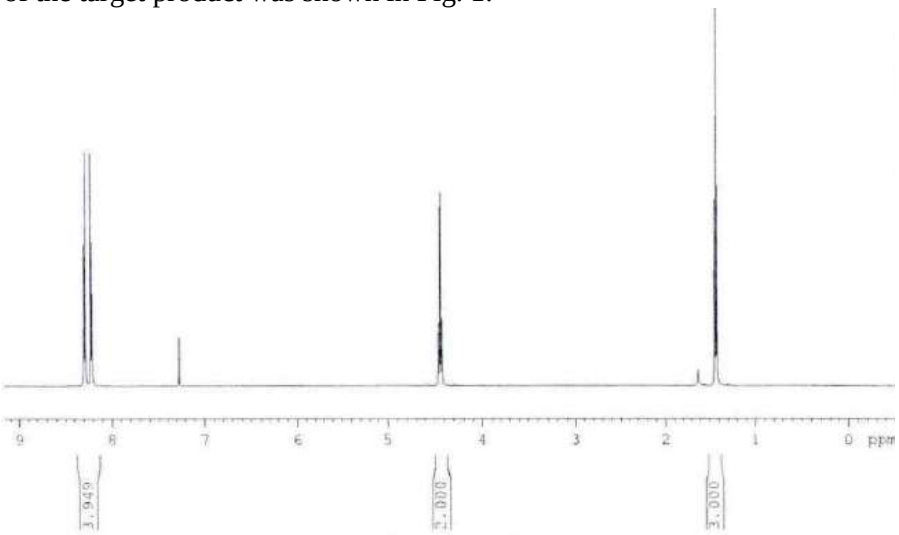

Fig. 1 HNMR spectrum of ethyl 4-nitrobenzoate

2.2.2. Synthesis of ethyl 4-(butylamino)benzoate 93.9g (0.48 mol) p-nitrobenzoate and 138.2 g (4.32 moles) methanol were added to a 1L four-necked flask equipped with a stirrer, a spherical condenser, a thermometer and a constant pressure dropping funnel. And then 38.1g (0.53 mol) n-butyraldehyde and 124.8g (1.92 mol) zinc powder were added there too. After cooling to 0-5℃, 230.4g (3.84 mol) acetic acid was added to the system with 0.5h. And then room temperature reaction and TLC tracking reaction stared, and this process spent about 2h. After the reaction, light brown yellow transparent liquid can be obtained by direct pumping, and the filter cake was washed with water (50 mL × 3). In addition, the generated salt was removed and the zinc powder was recovered.meanwhile, the mother liquor obtained by suction filtration was evaporated under reduced pressure and the methanol was used for recovery. The remaining part was dissolved using 200mL ethyl acetate, and the salt and acetic acid were removed by washing. And then the organic phase was dried. 100.8g ethyl p-butylaminobenzoate crude can be obtained with 94.7% yield. The target product of nuclear magnetic resonance spectrum was shown in Fig. 2.

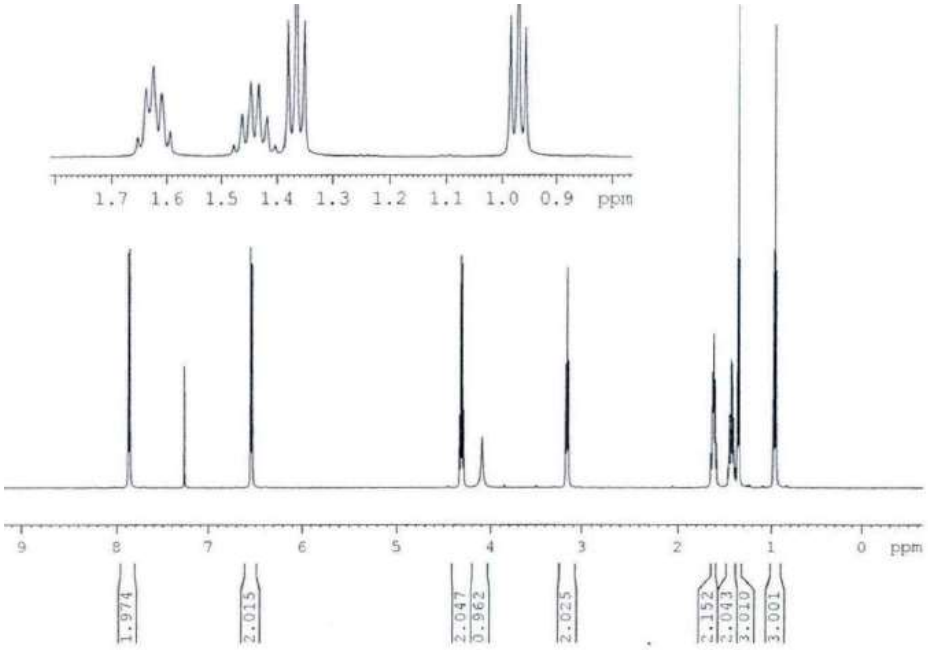

Fig. 2 HNMR spectrum of ethyl 4-(butyl amino) benzoate

3. Results

(1) The synthesis of p-nitrobenzoic acid ethyl acetate: The p-nitrobenzoic acid was selected as raw material and ethanol vinegar in this reaction under the temperature of 80℃. In addition, potassium hydrogen sulfate was taken as a catalyst, p-nitrobenzoic acid, ethanol, and the optimum reaction molar ratio of p-nitrobenzoic acid, anhydrous ethanol and potassium hydrogen sulfate was 1: 5: 0.1. The reaction yield was 3%, and the final yield was 96.3%. It was a simple acetic acid reaction with high yield. After cooling, the low concentration of sodium carbonate was added to remove the p-nitrobenzoic acid, filter, drying and the drying product p-nitrobenzoic acid.

(2) Synthesis of p-butylbenzoic acid and acetylene: The optimum reaction molar ratio of p-nitrobenzoic acid ethyl acetate, n-butyraldehyde, zinc powder and acetic acid was 1:1.1:4:8 at the temperature of 25℃. And the reaction yield was 94.7%. The reaction time is short, and the condition is mild. The product is simple after the reaction. The filter work was completed after the reaction. Meanwhile, the excess zinc powder can be washed, and the oxide layer can be removed through acidification. The zinc power can be recycled after the drying, while the application effect was better. However, the mother liquor is filtered under reduced pressure, which can recover methanol with 80% recovery rate.

4. Conclusion

In this paper, tetracaine hydrochloride is studies as a local anesthetic. It is widely used in clinic, which is often used for surface, infiltration and other local anesthesia. There are few manufacturers of tetracaine hydrochloride in the domestic market, and most of tetracaine hydrochloride products in the market come from abroad. The domestic production is far from meeting the market demand, and there are many problems existing in the production process, such as low yield, high cost, and harsh conditions and so on. By verifying the feasibility of the original route, a new synthetic route is proposed according to the experimental conditions. The synthetic route was optimized, and the effects of reaction factors on the reaction were determined by repeated experiments. Combined with the actual production conditions of industrialization, the industrial production line is determined. Compared with the prior art, the method has the advantages of low cost, easy and safe operation, low requirement of reaction equipment, low cost, short production period, high yield and high purity. Reagents that are less harmful to the

environment are selected as far as possible in the reaction process. These measures reduce the harm to the human body. The raw materials are cheap and the production cost is reduced. According to the experimental reagent, the reaction device is simplified to make it easier for industrial production. From the whole synthetic route, this kind of synthetic process is suitable for industrial production.

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