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An Efficient and Practical Synthesis of Ropivacaine Hydrochloride under Ultrasound Irradiation

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SUMMARY. Ropivacaine hydrochloride was synthesized from L-2-pipecolic acid by successive reaction with SOCl2 and 2,6-dimethylaniline at 40 °C under ultrasonic irradiation to yield L-N-(2,6-dimethylphenyl)-piperidin-2-carboxamide (**4**), and **4** was reacted with 1-bromopropane at 50 °C for 1 h under ultrasonic irradiation. The effects of reaction solvent, temperature and time under ultrasonic irradiation were investigated. Compared with conventional methods, present procedures have the advantages in milder conditions, shorter reaction time and higher yields. The total yield was 67.5%, [α]25 D= - 6.6°(c = 2, H_2O).

INTRODUCTION

Sonochemistry is a new trend in organic synthesis [1], offering a versatile and facile pathway for a large variety of syntheses. Thus, a large number of organic reactions can be carried out under ultrasonic irradiation, which has advantages in high yields, short reaction time and mild reaction conditions [2-7].

Ropivacaine (L-*N*-n-propylpipecolic acid-2,6-xylidide) is a long-acting aminoamide local anaesthetic. Compared with other amide-type local anaesthetics, ropivacaine has longer anaesthesia time and less toxicity in the cardiovascular and central nervous systems. Ropivacaine is usually indicated for local anaesthesia including infiltration, nerve block, epidural and intrathecal anaesthesia [8-10].

Ropivacaine can be obtained by many methods [11-14]. It is universally acknowledged that the acetyl chloride method is a major approach to commercial production [11]. Zavareh & Frampton [12] adopted thionyl chloride as the chlorinating agent. This method is economical and the afterprocessing is simple. However, the intermediate compound L-2-pipecolic chloride is a very labile substance and may be decomposed upon exposure to atmospheric moisture. Elevation of temperature to 70 °C will accelerate its decomposition. Therefore, it is necessary to find a new way of reaction under mild conditions and with a good yield. Ultrasonic irradiation can accelerate organic reactions by cavitational effect [15], especially in heterogeneous reactions. The cavitational effect can sufficiently reduce reaction temperature. The ultrasound approach is superior to conventional reaction methods for its energy conservation and atom economy [16]. We report a simple, mild and expeditious synthesis of ropivacaine hydrochloride with high yields under ultrasonic irradiation (Fig. 1).

MATERIALS AND METHODS

Reagents and analysis

Melting points were measured with an XRC-1 melting point apparatus. Optical rotation measurements were performed on a Perkin-Elmer model 341 automatic polarimeter. ^{1}H-NMR spectra were recorded using a Bruker Avance 400 (400 MHZ) spectrometer for solutions in DMSO and $CDCl_3$ with tetramethylsilane as internal standard. The chemical shifts were given in ppm and coupling constants were in Hertz. Mass

KEY WORDS: Local anaesthetic, L-2-pipecolic acid, Ropivacaine, Sonochemistry.

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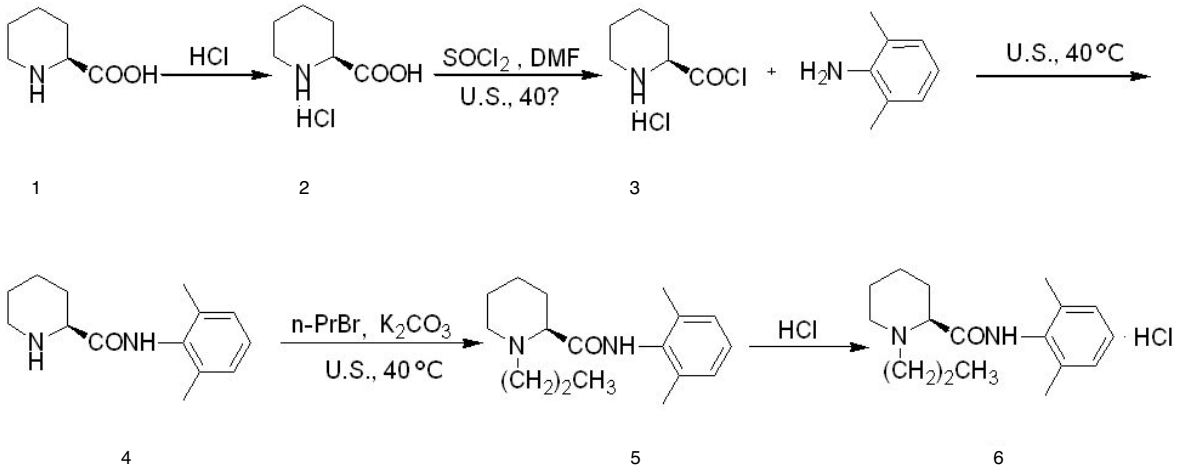

Figure 1. The synthetic route of ropivacaine hydrochloride.

spectra were obtained using Agilent 6460 with electron spray ionisation. Sonication was performed in Ningbo SB-5200D ultrasonic cleaner (at a frequency of 40 kHz and a nominal power 300 W). The reaction flask was located in the ultrasonic bath, with the surface of reactants slightly lower than the level of the water. The reaction temperature was controlled by the addition or removal of water from ultrasonic bath. The main reactants included 2-pipecolic acid and thionyl chloride (Dongguan Sinopharm Group, China). The other raw materials and solvents were purchased from their respective suppliers and underwent no further purification. Distilled water was self-prepared in our laboratory.

General procedures for the synthesis of (S)-pipecolic acid-2,6-xylidide

A suspension of L-pipecolic acid (6.5 g, 0.5 mol) was prepared in chloroform (100 mL). Dry hydrogen chloride gas was slowly introduced into the stirred solution at ambient temperature for 1 h. Thereafter, the solution was filtered and the filter cake was air-dried at 60 °C for 5 h. The intermediate **2** was suspended in dry toluene (100 mL). The reaction mixture was irradiated under ultrasound at 40 °C, and dimethylformamide (1 mL) was added, followed by the addition of thionyl chloride (5.4 mL, 0.075 mol) within 10 minutes. 1.5 hs later, 2,6-dimethylaniline (32.5 mL, 0.25 mol) in toluene (10 mL) was slowly added to the mixture. The reaction mixture was irradiated with ultrasound at 40 °C for 2 h. At the end of the reaction, the mixture was filtered for the collection of the solid product, which was then rinsed with acetone (5 mL) to obtain beige solid. The solid was dissolved in water (120 mL) and was treated with 1 M NaOH, with the pH value of the solution raised to 6-7. The liberated 2,6-dimethylaniline was removed by extraction with toluene (100 mL × 3). Subsequently, the pH value of the aqueous layer was adjusted to 11-12, and the solid product in the solution was extracted by toluene (100 mL × 3). The combined organic layers were rinsed with water and saturated NaCl saline, and then dried with Na_2SO_4, followed by concentration under negative pressure to yield the white solid **4**.

General procedures for the synthesis of ropivacaine hydrochloride

N-propyl bromide (2.6 mL, 0.023 mol) and K_2CO_3 (4.2 g, 0.025 mol) were added to a solution of **4** (5.8 g, 0.021 mol) in dimethylformamide (15 mL). The reaction mixture was irradiated with ultrasound at 40 °C for 1 h. The process of reaction was monitored by TLC (*n*-hexane-EtOAc, 1:1). At the completion of the reaction, the reaction mixture was poured into ice water (60 mL) and stirred vigorously for 20 min. Then, the product was filtered and the filter cake was rinsed with water (10 mL × 3). Dry hydrogen chloride gas was slowly introduced into the **5** solution with isopropanol (30 mL) as the vehicle at ambient temperature for 15 min. The resulting white product was filtered off, rinsed with isopropanol (10 mL) and dried in vacuum to obtain the desired product **6**.

Spectral Date for the Selected Compounds

(S)-pipecolic acid-2,6-xylidide

Yield 72.4%, m.p.128.3 -129.8 °C (Lit. [11] m.p.

129 to 130 °C). $[\alpha]_D^{20}$ = + 46.4° (c = 2, 1 M HCl). ^{1}H NMR (DMSO): 1.42-1.86 (m, 6H, 3-H, 4-H_2, 5-H_2, 6-H on piperidine), 2.12(s, 6H, $C_6H_3(CH_3)_2$), 2.51(m, 1H, NH on piperidine), 2.56-2.62 (m, 1H, 3-H on piperidine), 2.97-3.00 (m, 1H, 6-H on piperidine), 3.27-3.36 (m, 1H, 2-H on piperidine), 7.05-7.08(m, 3H, Ar-H), 8.25 (s, 1H, CONH). ESI-MS: 231.1 ($[M+H]^+$).

Ropivacaine hydrochloride

Yield 93.2%, m.p. 259.2-262.4 °C (Lit. [11] m.p. 260-262 °C); $[\alpha]_D^{25}$ = -6.6°(c 2, $H_2O)_o$ ^{1}H NMR($CDCl_3$): 0.91-0.95 (t, 3H, $CH_2CH_2CH_3$), 1.34-1.77(m, 7H, 3-H, 4-CH2, 5-CH2 on piperidine, $CH_2CH_2CH_3$), 2.03-2.24 (m, 3H, 6-H on piperidine, N-CH2), 2.22 (s, 6H, C6$H_3(CH_3)_2$), 2.79-2.88 (d, 1H, 3-H on piperidine), 2.88-2.91 (d, 1H, 6-H on piperidine), 3.21-3.24 (t, 1H, 2-H on piperidine), 7.10-7.28 (m, 3H, C_6H_3), 8.17 (s, 1H, CONH). ESI-MS: 274.2 ($[M+H]^+$).

RESULTS AND DISCUSSION

Effects of organic solvents

In this experiment, we observed the effects of the organic solvents as follows (toluene, tetrahydrofuran, acetonitrile, benzene or dichloromethane) on the yield of **4** under other reaction conditions (Table 1).

We noted that the highest yield was achieved with toluene. When the reaction was performed in solvents acetonitrile, benzene and dichloromethane, the yield of the desired product **4** was only 15.2, 62.1, and 56.3%, respectively. In the solvent tetrahydrofuran, no yield of the product was obtained. We supposed that tetrahydrofuran takes part in the prosess of the reaction in acid environment by ring-opening reaction. Therefore, toluene was sieved as solvent of reaction.

The effects of temperature and time of the chlorination reaction under ultrasonic irradiation

In this nucleophilic substitution reaction, chloridion attacks the carbon atom of the carboxyl group and hydroxyl is the leaving group.

Items	Solvents	Yields (%)
1	toluene	70.5
2	tetrahydrofuran	0
3	acetonitrile	15.2
4	benzene	62.1
5	dichloromethane	56.3

Table 1. Influence of organic solvents on the yield of **4** under ultrasonic condition.

L-pipecolic acid chloride (**3**) is a key intermediate of the chlorination reaction. However, temperature elevation will accelerate its decomposition, and thus it is necessary to search for a mild method for the synthesis of **3**. The reaction time ranged from 0.5 to 2.5 h. In order to get the optimal reaction temperature, five experiments at 20, 30, 40, 50, and 60 °C under ultrasonic irradiation (Fig. 2) were performed. It was observed that higher yields were obtained with higher temperatures, such as 20, 30, and 40 °C. The highest yield was got at 1.5 h. When the temperature was over 40 °C, such as 50 and 60 °C, the yield was reduced due to the production of side reaction. These results indicated a remarkable ultrasonic temperature effect on this reaction. Compared with conventional methods, it was clear that the ultrasound could accelerate the reaction of L-pipecolic acid and thionyl chloride.

The effects of reaction temperature and time on the synthesis of 4

To investigate the effect of temperature and time on the synthesis of **4**, the reaction was performed at temperatures ranging from 20 to 60 °C, and the time was set from 1 to 3 h (Fig. 3). The highest yield was obtained at 40 °C, and the optimal reaction time was 1.5 h. In this experiment, we also attempted to verify the optimal condition for stereospecific synthesis of ropivacaine (Fig. 4). When the temperature was below 40 °C, the racemisation rate showed no significant variation. Higher racemisation rates were observed at higher temperature, such as 50 and 60 °C. We presumed that higher temperature promoted the racemisation reaction [17].

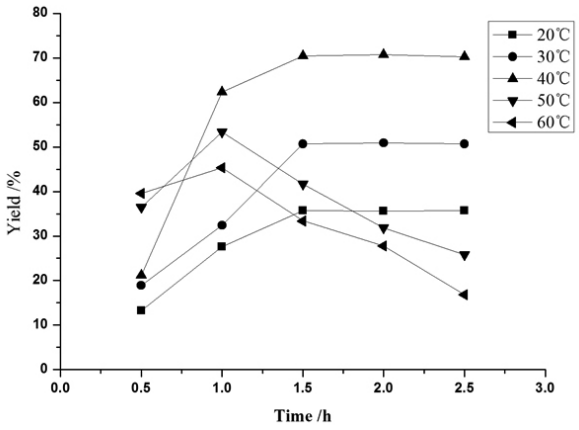

Figure 2. The effect of temperature and time of the chlorination reaction under ultrasonic irradiation.

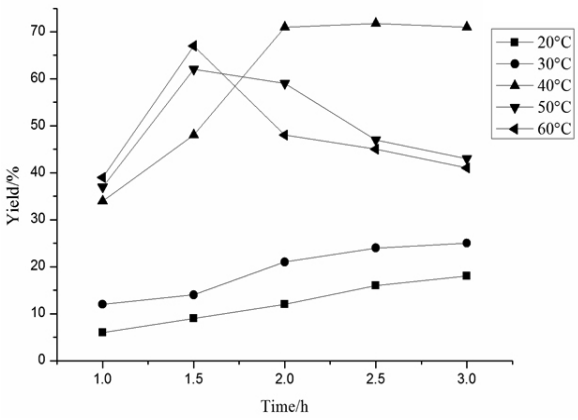

Figure 3. The effect of temperature and time of the amidation reaction under ultrasonic irradiation.

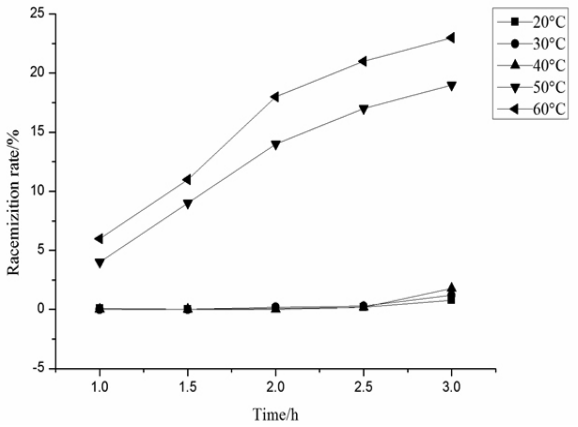

Figure 4. The effect of temperature and time on the racemisation rate of **4**.

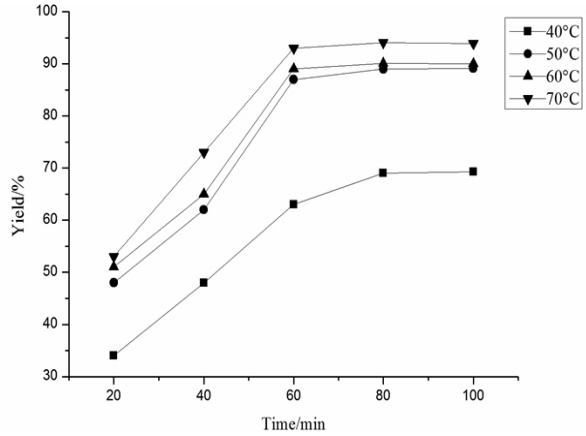

Figure 5. The effects of temperature and time on the yields of **5** under ultrasonic irradiation.

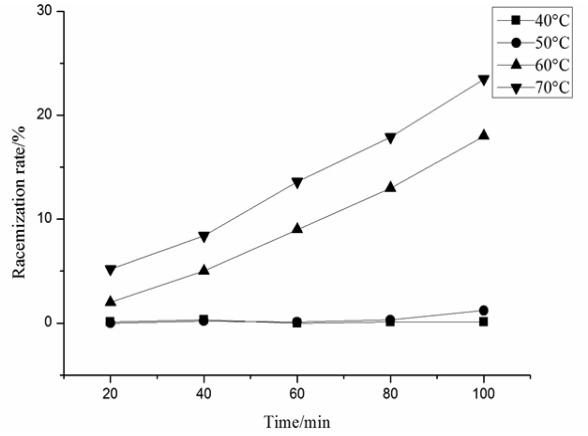

Figure 6. The effect of temperature and time on the racemisation rate of **5**.

The effects of temperature and time on the synthesis of 5

First, we verified the effects of temperature and time on the yields of **5** (Fig. 5). When the reaction time ranged from 20 to 60 min, the yield of **5** gradually increased. With prolonged time, such as 80 and 100 min, the yield had no remarkable variation. The yield increased as the temperature was raised from 40 to 70 °C, and the racemisation rate of **5** was measured (Fig. 6). The racemisation reaction of **5** was mainly at 60 and 70 °C, with no significant variations at 40 and 50 °C. On the basis of the above results, the propyl reaction at 50 °C was performed for 60 min.

CONCLUSION

In summary, we have developed an effective method for the synthesis of ropivacaine hydrochloride under ultrasound irradiation. This new method offers several advantages such as higher feasibility, shorter reaction time and milder conditions. In addition, this method is also applicable to the preparation of bupivacaine and mepivacaine, for their common intermediate **4**.

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