The preparation of a kind of phenylephrine intermediates

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Abstract. A two-step method to accomplish the synthesis of the important intermediate \( \alpha \)-\((N\text{-methyl-N-benzylamino})\)-3-hydroxy acetophenone hydrochloride was discussed, including a bromination and the following amination. Starting from the commercial available raw material, the target compound could be gained with 62% yield. This procedure involves cheap and easily obtained raw materials, simple operation, low cost, low waste production.

1. Introduction

Phenylephrine is an \( \alpha_1 \)-adrenergic receptor agonist of the phenethylamine class, and is primarily used as a decongestant[1] for bronchiectasis and vascular contraction nasal mucosa. It can reduce nasal and sinus congestion relieve nasal mucosal hyperemia or swelling, and may also relieve symptoms of nasal congestion. This supplement can also be used to treat shock and supraventricular tachycardia, or used to maintain blood pressure during anaesthesia and mydriatic check[2,3]. Phenylephrine initially by the Frederick Stearns company, was successfully developed in 1934. For a long time, the use of the compounds by Aspirin, Phenylpropanolamine Hydrochloride, dextral ephedrine, and some other related compounds. The dosages of the pharmaceuticals in our country are relatively small, for many years in the domestic production technology research and preparation research basically is in a state of stagnation.

There is vast social significance in our country pushing to catalyze the related research and application of phenylephrine, instead of continuing to use similar compounds, especially in the...
treatment of flu and related diseases of drug use to improve the level of people's rational drug use, and inhibit drug related crimes.

Various synthesis studies and findings regarding phenylephrine have been reported [4-6], but only a few are of industrial value. (R)-phenylephrine hydrochloride (figure 1) is the common form of phenylephrine in the pharmaceutical industry. α-(N-methyl-N-benzylamino)-3-hydroxy acetophenone hydrochloride (b) is a key intermediate to accomplish the synthesis of (R)-phenylephrine hydrochloride. Magnificently, after an asymmetric hydrogenation process, (R)-phenylephrine hydrochloride can be produced. There are many preparation methods for the intermediate or similar intermediates. In this study, we have developed a simple operation, promoting an energy saving synthesis method on the basis of previous studies, for a total of two steps bromination and amination.

2. Bromine generation reaction to obtain α-bromo-3-acetoxy acetophenone

Traditional bromine generation reaction[7-9], is a free radical substitution reaction between bromine and the substrate. Considering hydrogen bromide generated in bromine generation reaction could be oxidized into bromine again, the new generated bromine will attend the bromination reaction again, so that we can improve the utilization rate of bromine to reduce costs.

| Table 1. Screening of reaction conditions for bromine generation reaction. |
|---|---|---|---|---|---|---|
| Entry | Br₂ | HBr | H₂O₂ | solvent | T/°C | Yield[%] |
| 1 | 1.1 | 0 | 0 | n-Butyl acetate | -5 | 0 |
| 2 | 1.1 | 0 | 0 | n-Butyl acetate | 0 | 83.7 |
| 3 | 1.1 | 0 | 0 | n-Butyl acetate | 10 | 75.9 |
| 4 | 1.1 | 0 | 0 | n-Butyl acetate | 20 | 73.8 |
| 5 | 1.1 | 0 | 0 | ethyl acetate | 0 | 76.2 |
| 6 | 1.1 | 0 | 0 | isopropyl acetate | 0 | 73.7 |
| 7 | 1.1 | 0 | 0 | CH₂Cl₂ | 0 | 68.4 |
| 8 | 1.1 | 0 | 0 | THF | 0 | 62.5 |
| 9 | 1.1 | 0 | 0 | n-Butyl acetate | 30 | 65.9 |
| 10 | 0 | 1.3 | 1.3 | n-Butyl acetate | 0 | 0 |
| 11 | 0.2 | 1.0 | 2.0 | n-Butyl acetate | 0 | 18.9 |
| 12 | 0.4 | 0.4 | 0.8 | n-Butyl acetate | 0 | 39.7 |
| 13 | 0.6 | 0.2 | 0.7 | n-Butyl acetate | 0 | 62.3 |
| 14 | 0.7 | 0.2 | 0.6 | n-Butyl acetate | 0 | 76.5 |
| 15 | 0.7 | 0 | 0.6 | n-Butyl acetate | 0 | 75.7 |
| 16 | 0.8 | 0 | 0.5 | n-Butyl acetate | 0 | 82.2 |
| 17 | 0.8 | 0 | 0.5 | n-Butyl acetate | 0 | 73.6 |

*aReaction conditions: Step 1) c (1.0 mmol), Br₂ (0.8 mmol), solvent 20 mL,1h; then; Step 2) H₂O₂ (0.5 mmol) 4h.

*bIsolated yield, including 3-(2,2-dibromoacetyl) phenyl acetate which could also be transformed into the target product in the next reactions. KMnO₄ is instead of H₂O₂.

First, we began by screening the reaction temperature and solvent, as illustrated below in table 1. It can be seen that the freezing point and n-Butyl acetate is at the most suitable conditions (entry1-8). The presence of hydrogen peroxide can reduce the necessary usage
amount of bromine (entry 2 and 16), however only hydrogen bromide and hydrogen peroxide can't cause bromination (entry 10). Other antioxidants can be tried, perhaps to the cause of the low dissolvability, however the product yield wasn't improved with the presence of KMnO₄ (17).

3. Amination reaction for α-(N-methyl-N-benzylamino)-3-hydroxy acetophenone hydrochloride

The reaction included two steps: the first amination, and the second the addition of acid to generate the salt. The whole process does not need to a chromatography column. The was generated by salt precipitation from the organic solvent, then (through recrystallization) can be the product as pure as a white powder. It's the better to choose an inorganic base to absorb acid (entries 1-6 in table 2). The reaction prefers aprotic solvents consistent with the previous reaction, therefore we chose n-butyl acetate as the solvent. The yield is exemplary at 20°C to 40°C, so the operation is convenient.

Table 2. Screening of reaction a conditions for α-(N-methyl-N-benzylamino)-3-hydroxy acetophenone hydrochloride.

| Entry | Base      | Solvent        | T/°C | Yield[%]  |
|-------|-----------|----------------|------|-----------|
| 1     | Na₂CO₃    | n-Butyl acetate| 30   | 73.5      |
| 2     | K₂CO₃    | n-Butyl acetate| 30   | 58.2      |
| 3     | NaHCO₃   | n-Butyl acetate| 30   | 63.7      |
| 4     | NaOH      | n-Butyl acetate| 30   | 66.8      |
| 5     | Et₃N     | n-Butyl acetate| 30   | 43.6      |
| 6     | pyridine  | n-Butyl acetate| 30   | 32.1      |
| 7     | Na₂CO₃    | ethyl acetate  | 30   | 70.3      |
| 8     | Na₂CO₃    | isopropyl acetate| 30 | 72.0      |
| 9     | Na₂CO₃    | CH₂Cl₂         | 30   | 68.5      |
| 10    | Na₂CO₃    | THF            | 30   | 62.3      |
| 11    | Na₂CO₃    | n-Butyl acetate| 20   | 72.8      |
| 12    | Na₂CO₃    | n-Butyl acetate| 40   | 71.4      |
| 13    | Na₂CO₃    | n-Butyl acetate| 50   | 70.4      |

aReaction conditions: Step 1) d(1.0 mmol), Na₂CO₃ (2.0 mmol), CH₃NHBN (1.1 mmol), solvent (20 mL), 2 h; then Step 2) concentrated hydrochloric acid (3 mmol), 2 h.

bIsolated yield from c to b. Et₃N= triethylamine.

4. Preparation method of phenylephrine

Results of asymmetric hydrogenation of α-(N-methyl-N-benzylamino)-3-hydroxy acetophenone hydrochloride(b) to get (R)-phenylephrine hydrochloride (a) [10] by using different catalysts has been reported, however here, we introduce the reaction using Ru(Ⅱ)-(R)-BINAP as the catalyst, which could be bought from any market. The reaction was conducted in an Argonaut Technologies, α-(N-methyl-N-benzylamino)-3-hydroxy acetophenone hydrochloride(b), and a catalyst was placed in a 100ml Parr autoclave with an overhead stirrer, and a heating jacket under the nitrogen atmosphere in figure 2. Methanol was added through the injection port, and the reaction was purged five times by pressurizing to 30 bar hydrogens and releasing the pressure while stirring. The reaction was then pressurized to 30 bar hydrogens and stirred at room temperature for over 45 hours. Then, the reaction
system was filtered, and evaporated under reduced pressure which gave off a white solid residue. After, recrystal from methanol the pure product was secured. The details were as follows: Purity: 98%, enantiomeric purity: 75%ee.

![BINAP structure](image)

**Figure 2. Asymmetric hydrogenation to get (R)-phenylephrine hydrochloride**

5. Summary

A method was developed to synthesize the α-(N-methyl-N-benzylamino)-3-hydroxy acetophenone hydrochloride; the important intermediate included two steps. In the first step, we used H₂O₂ oxidize HBr to reduce the consumption of expensive bromide. The two steps are merged into one after adding a concentrated hydrochloric acid product. The product precipitated from the organic phase in high yield. Then, the product could be purified by recrystallization.

6. Experimental section

**d**: Br₂ (128 mg, 0. 8 mmol) was slowly dropped into a solution of c(1.78 g, 1.0 mmol) in n-Butyl acetate (20mL) in a 50 mL flask, which was equipped with a stirrer bar. The reaction mixture was stirred for 1 hour in an ice-water bath. Then, 30% H₂O₂ (56.8 mg, 0. 5 mmol) was dropped into the solution slowly. After stirring for another 4 hours in the ice-water bath. The resulting mixture was quenched with water and extracted with EtOAc. The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure to produce d as a crude product of yellow oil (2.80g, >100%).

**b**: To the solution of d (2.8 g) in n-Butyl acetate (20 mL) the solution of Na₂CO₃ (212 mg, 2 mmol) in water (5 mL) was successively dropped, then the CH₃NHBn (233 mg, 1.1 mmol) was dropped into the solution. The reaction mixture was stirred for 2 hours at room temperature. The resulting mixture was extracted with n-Butyl acetate (10 mL) and cleansed with saturated sodium chloride. Then, to the combined organic layers concentrated hydrochloric acid (0.25 mL, 3 mmol) was dropped. Combined acid water layers and washed with n-Butyl acetate. Acid water was heated up to 40 ~ 45℃, then the temperature was kept for 2 hours, and cooled to the temperature of 0℃. The product was precipitated as a white solid, after recrystallization in acetone obtained the pure product,b (143g, 62%).

1H NMR (500 MHz, CDCl₃) δ 8.05(s, 1H), 7.53 (s, 1H), 7.43 (s, 1H), 7.37 (s, 1H), 7.29 – 7.17 (m, 5H), 7.01 (s, 1H), 5.66 (s, 1H), 4.32 (s, 1H), 3.89 (s, 1H), 3.57 (s, 1H), 3.48 (s, 1H), 2.34 (s, 3H). ESI-MS: 256.3.

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References

[1] 2006 The Merck Index 14th ed (NJ, USA: Merck and Co., Inc.: Whitehouse Station)
[2] John F McGarrity 2010 Tetrahedron: Asymmetry 21 2479-86
[3] Helmut Legerlotz 1933 Beta-alkyl-amino compounds Of Mono-hydroxy-phenyl-ethanols and process of producing same US 1932347 Oct 24
[4] Hukki Jaakko and Honkanen Erkki 1959 Acta Chemica Scandinavica., 13 329-32
[5] H. Takeda, T. Tachinami, M. Aburatani, H. Takahashi, T. Morimoto, K. Achiwa.1989 Tetrahedron Lett. 30 367-70
[6] S. SAKURABA, H. TAKAHASHI, H. TAKEDA, K. ACHIWA,1995 Chem. Pharm. Bull. 43 738-47
[7] Helmut Legerlotz 1934 Process of manufacturing optically active mono-hydroxyphenyl methylamino-ethanols-1 US 1954389 Apr 10
[8] Divi Murali Krishna Prasad 2012 Process for resolution Of 1-(3-hydroxyphenyl)-2-methylamino ethanol, US2012/0108848 May 3
[9] Breuer Michael and Pletsch Andreas 2010 Method for producing L-phenylephrine using an alcohol dehydrogenase of aromatoleum aromaticum Ebn1 (azoarcus Sp. Ebn1) WO2010/031776 A3 Sep. 10
[10] Feng Wenhua, Guo Fangchao and Yu Xiaoli 2011 Preparation methods Of L-phenylephrine hydrochloride, WO2011/131027 Oct. 27