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The preparation of 8-[4-[4-(2-pyrimidinyl)-1-piperaziny]butyl]-8-azaspiro[4,5] decane-7,9-dione hydrochloride

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Abstract 8-[4-[4-(2-Pyrimidinyl)-1-piperaziny]butyl]-8-azaspiro [4,5] decane-7,9-dione hydrochloride (buspirone hydrochloride) was obtained in one pot with a 51.8% overall yield. The key intermediate, 1-(2-pyrimidinyl) piperazine, was synthesized through chlorination and cyclization condensation reaction with diethanolamine as initial material. This modified protocol has the notable advantages of mild reaction condition, convenient operation, and high overall yield.

Keywords Buspirone hydrochloride · Diethanolamine · Cyclization · One-pot synthesis method

Introduction

Buspirone hydrochloride, 8-[4-[4-(2-pyrimidinyl)-1-piperaziny] butyl]-8-azaspiro [4,5] decane-7,9-dione hydrochloride (**3**) is widely used in therapy as an efficient antianxiety compound [1]. Buspirone hydrochloride's clinical efficacy is similar to diazepam, but it does not suffer from the usual side effects of benzodiazepines, namely sedation and addiction [2–5].

Scheme 1 summarizes the general methods of synthesis employed for buspirone hydrochloride, all syntheses are based on three fragments [6–8]: 1-(2-pyrimidinyl)

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piperazine (**i**), substituted imide or anhydride (**ii**), and four-carbon aliphatic chain (**iii**). This type of synthesis is mainly done in two steps: coupling of the four carbon chain **iii** with one of the fragments **i** or **ii** followed by attachment of the second unit **ii** or **i**, respectively. Due to the complex operation, poor industrialized efficiency has existed in the total synthesis of buspirone hydrochloride. In addition, 2-chloro-pyrimidine, the raw materials of **i**, was obtained through diazotization from 2-amine-pyrimidine and excessive zinc chloride with a poor yield less than 60%, and the excessive zinc chloride caused serious pollution [9]. Thus, the complex operation and the preparation of **i** contributed to the poor overall yield and high production cost of the whole procedure.

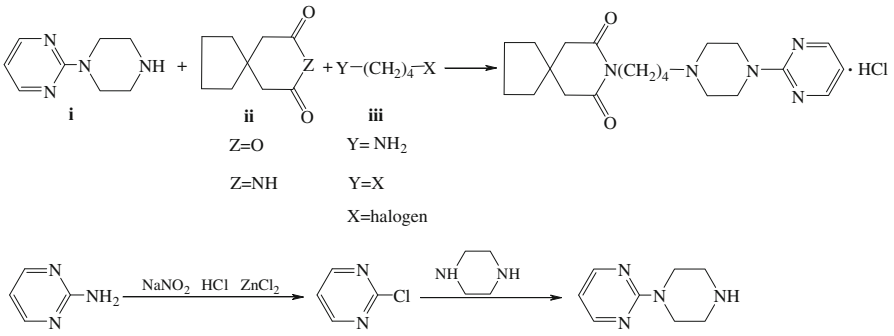
In this article, great efforts were made to simplify the synthesis routine of buspirone hydrochloride as shown in Scheme 2. The key intermediate 1-(2-pyrimidinyl) piperazine (**2**) was synthesized from diethanolamine in high yield of 76.9%, and the preparation of compounds **2**, **3** were done in one pot with high yield. This procedure of *N*-alkylation reaction indicates a great deal of value for the notable advantages of high overall yield, readily available raw materials and convenient operation.

Experimental procedure

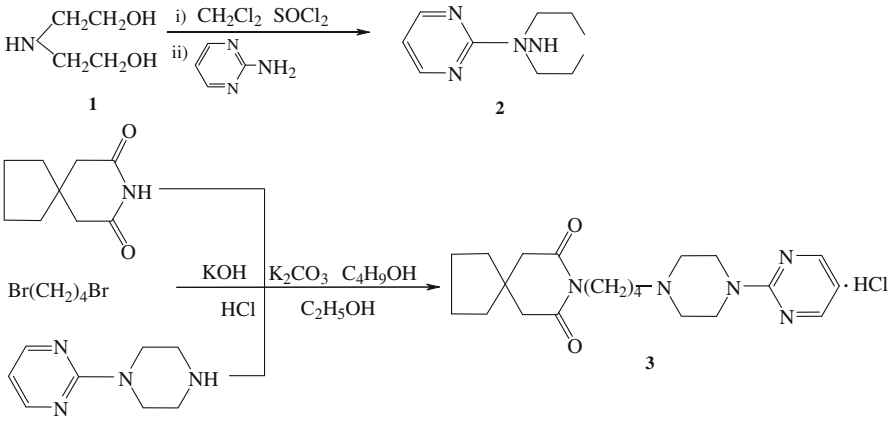
Melting points were determined on a WSR-I capillary melting point apparatus and are uncorrected. IR spectras were record on Nicolet EST 560 spectrometer in KBr with absorption in cm^{-1}. ^1H NMR spectras were measured on a Bruker 400 MHz spectrometer in $CDCl_3$ with TMS as internal standard. All the reagents used in the experiments were analytical reagents.

1-(2-Pyrimidinyl) piperazine (2)

Diethanolamine (25 g, 0.24 mol) was dissolved in dichloromethane (30 mL, 0.47 mol), and dichloro sulfoxide (70 mL, 0.96 mol) dissolved in dichloromethane



Scheme 1 General methods of synthesis employed for buspirone hydrochloride



Scheme 2 Simplified synthesis routine of buspirone hydrochloride

(45 mL, 0.70 mol) was gradually added. The mixture was stirred at 25–30 °C for 1 h and then heated to reflux for 0.5 h. After cooling, the solid was filtered off and washed with dichloromethane, and 90% of the solvent was recovered. This material was dried, then dissolved in butanol (92 mL, 1.0 mol) and anhydrous potassium carbonate (30.53 g, 0.22 mol) was added. Following the gradual addition of 2-amino-pyrimidine (21.1 g, 0.22 mol), the mixture was refluxed for 8 h, after which time the starting material had been consumed as evidenced by TLC (developing solvent, EtOAc/petroleum ether = 1:1, V/V) analysis. The resulting slurry was filtered and concentrated. The thick oily residue was fractionated under reduced pressure to give the target **2** (32.5 g, 76.9%), BP 115–117 °C (133 Pa), lit [10]. BP 118–120 °C (270 Pa). IR (KBr), ν cm^{-1}: 3422, 1629, 1230. ^1H NMR ($CDCl_3$): δ 2.08 (bs, 1H, N–H), 2.82 (m, 4H, 2× CH_2), 3.58 (t, 4H, 2× CH_2), 6.74 (t, 1H, Ar–H), 8.41 (d, 2H, Ar–H).

8-[4-[4-(2-Pyrimidinyl)-1-piperaziny]butyl]-8-azaspiro[4,5] decane-7,9-dione hydrochloride (3)

β,β'-tetramethylene glutarimide (30 g, 0.18 mol) was added to ethanol (45 mL, 0.78 mol), and potassium hydroxide (10.2 g, 0.18 mol) dissolved in ethanol (120 mL) was gradually added. The mixture was stirred at room temperature for 2 h and then the solvent was evaporated. The residue was treated with acetone to afford potassium compound. This material was gradually added to 1,4-dibromo-butane (108.0 g, 0.51 mol), and the mixture was stirred at 50 °C for 8 h. The resulting slurry was cooled, filtered and concentrated. Without purification, the residue was added to the solution of **2** (30.0 g, 0.17 mol), anhydrous potassium carbonate (70.5 g, 0.51 mol) and butanol (1100 mL, 12.0 mol). The mixture was refluxed for 15 h, after which time the starting material had been consumed as evidenced by TLC (developing solvent, EtOAc/petroleum ether = 1:1, V/V)

analysis. The solvent was evaporated under reduced pressure and the mixture was cooled. The solid was filtered off and dissolved in ethanol (56 mL). Then, hydrogen chloride gas was injected into the solution until crystalline powder was obtained. After cooling, the solid was filtered off and crystallized with ethanol to give the target **3** (51.2 g, 67.4%), MP 200–203 °C, lit [7]. MP 201–202 °C. IR (KBr), ν cm^{-1}: 2,951, 1,670, 1,635, 1,580, 1,484, 1,383, 953, 793. ^{1}H NMR ($CDCl_3$): δ 1.42 (m, 8H, 4× CH_2), 1.55 (m, 4H, 2× CH_2), 2.21 (m, 2H, CH_2), 2.47 (s, 4H, 2× CH_2), 2.72 (m, 4H, 2× CH_2), 3.97 (m, 6H, 3× CH_2), 6.71 (t, 1H, Ar–H), 8.40 (d, 2H, Ar–H).

Results and discussion

Improving the synthesis of buspirone hydrochloride presented some challenges. The simple operation and suitable synthetic protocol of 1-(2-pyrimidinyl) piperazine (**2**) were key issues. The 1-(2-pyrimidinyl) piperazine (**2**) was prepared in one pot over two steps with diethanolamine as raw material. Considering that the dropwise of dichloro sulfoxide caused a sharp reaction, a mixture of dichloromethane and dichloro sulfoxide was employed to keep the reaction under control, and 90% of the solvent was recovered. Without further purification, the intermediate β,β'-dihalogenated diethylamine was converted by cyclization condensation with 2-aminepyrimidine to **2** in a high yield of 76.9%. Compared with the corresponding product using 2-chloro-pyrimidine as starting material, this method not only gave a higher yield, but also with a eco-friendly and convenient operation.

According to the literature method [11], 8-(4-bromobutyl)-8-azaspiro [4,5] decane-7,9-dione was prepared from β,β'-tetramethylene glutarimide and 1,4-dibromo-butane at 180–190 °C for 20 h. We chose to firstly treat β,β'-tetramethylene glutarimide with potassium hydroxide to give the corresponding potassium salt, which was reacted with 1,4-dibromo-butane at 50 °C for 8 h to afford 8-(4-bromobutyl)-8-azaspiro [4,5] decane-7,9-dione by Gabriel reaction. Temperature played a really important role in this reaction, and the alkylation reaction was accelerated with serious side effects at high temperatures. After the potassium bromide and excess 1,4-dibromo-butane were separated, the residue was treated with 1-(2-pyrimidinyl) piperazine to afford buspirone hydrochloride in a yield of 67.4%.

Due to the high yield and convenient operation, the cost of buspirone hydrochloride decreased greatly by this method and will be suitable for substantive commercial production, and also provides the foundation for further efforts to increase access to it.

Conclusion

The synthesis of buspirone hydrochloride was improved by one-pot synthesis method with a 51.8% overall yield. The key intermediate 1-(2-pyrimidinyl) piperazine was synthesized in a higher yield from diethanolamine through

chlorination with dichloro sulfoxide and cyclization condensation with 2-amine-pyrimidine. Thus, we have succeeded in developing an improved synthesis route of buspirone hydrochloride characterized by cheap and readily available materials, convenient operation and high overall yield.

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