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Efficient synthesis of 3-(bromomethyl)-5-methylpyridine hydrobromide

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Abstract: 5-Methyl-3-(bromomethyl)pyridine is the key intermediate in the synthesis of rupatadine. In this article, a new preparation of 5-methyl-3-(bromomethyl)pyridine hydrobromide is reported, which used 5-methylnicotinic acid as the starting material, with a 65.9% overall yield. This method has the merits of being simple, efficient, and environmentally friendly.

Keywords: 3-(bromomethyl)-5-methylpyridine hydrobromide; 5-methylnicotinic acid; synthesis.

Introduction

3-(Bromomethyl)-5-methylpyridine (**5** in Scheme 1) is an important pharmaceutical intermediate of rupatadine [1], which is used in the treatment of seasonal and allergic rhinitis [2]. It has been reported that pyrazolopyrimidine derivatives substituted by a reaction with compound **5** show an increased activity against cancer and other diseases related to the dysregulation of cMet kinases (such as non-small-cell lung carcinomas, gastric and esophageal carcinomas) [3]. Related analogues are useful in the treatment of p38 kinase-mediated diseases (such as lymphoma and auto-inflammatory disease) [4].

It has been reported that 3,5-dimethylpyridine can be brominated in CCl_4 by treatment with *N*-bromosuccinimide to give compound **5** in a 50% yield [5]. It has also been reported that the yield for this reaction can be increased to 68% in the presence of azobisisobutyronitrile [6]. Lin and Xin [7] have analyzed these two synthetic methods and have shown that bromination of 3,5-dimethylpyridine is difficult to control and produces large amounts of dibromo-substituted compounds. Moreover, the mixture with unreacted 3,5-dimethylpyridine is difficult to resolve, and the yield of the desired mono-bromo product **5** is poor. A new synthetic approach to **5** has been reported using methyl 5-methylnicotinate as the starting material [3]. In our hands, the reported method has been unreliable and the use of $LiAlH_4$ makes it unsuitable for a large-scale industrial production.

In this article, we report a new synthesis of compound **5** with 5-methylnicotinic acid (**1**) as the starting material. This method is environmentally friendly and is suitable for a large-scale industrial production.

Results and discussion

In the first step, methyl 5-methylnicotinate (**2**) was obtained by reaction of **1** with methanol in the presence of thionyl chloride, which was used as a scavenger of water generated during the esterification reaction. The yield was 95.5%. Then the reduction of **2** carried out with sodium borohydride in methanol furnished (5-methylpyridin-3-yl)methanol (**3**). Lithium aluminum hydride can also be used as the reducing agent [8–11]; however, the use of $LiAlH_4$ is not suitable for a large-scale preparation. With sodium borohydride, regardless of the reaction scale, the conditions are mild and the preparation is not hazardous [12–14]. Compound **3** was obtained as a yellow oil that was difficult to purify. However, its hydrobromide salt **4** was easily purified by simple crystallization from a mixture of tetrahydrofuran and ethanol. The overall yield of the two steps indicated above was 85%. The desired product **5** was obtained by treatment of compound **4** with hydrogen bromide in xylene. The high yield of 79.5% was due to the azeotropic removal of water generated during the reaction.

Conclusion

3-(Bromomethyl)-5-methylpyridine bromide (**5**) was obtained in an overall yield of 66% of a four-step procedure

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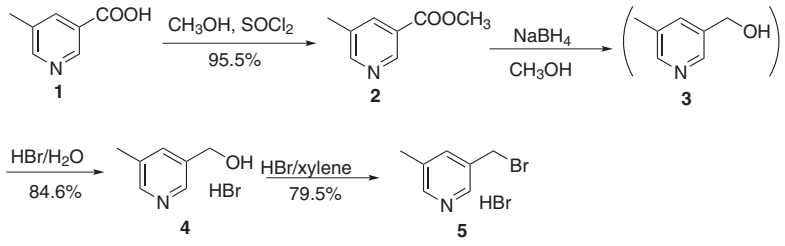

Scheme 1

starting with 5-methylnicotinic acid. This method is environmentally friendly and is suitable for a large-scale industrial production.

Experimental details

^{1}H NMR spectra (400 MHz) were recorded on a Bruker AV 400 spectrometer. Mass spectra were acquired in a positive mode using a mass spectrometer equipped with electrospray ionization (ESI) source. FT-IR spectra were obtained on an Avatar360 spectrometer.

Methyl 5-methylnicotinate (2)

Thionyl chloride (110 mL, 1.50 mol) was added dropwise to a solution of 5-methylnicotinic acid (**1**, 102.8 g, 0.75 mol) in methanol (500 mL) under a nitrogen atmosphere at 20–25°C, and then the mixture was heated under reflux for 4 h. After completion of the reaction, as monitored by TLC, methanol was removed under a reduced pressure and the residue was treated with cold water (200 mL). The mixture was neutralized by addition of saturated sodium carbonate solution and extracted with ethyl acetate (2×250 mL). The extract was washed by brine, dried with anhydrous sodium sulfate, filtered, and concentrated under a reduced pressure. Compound **2** as obtained as a white solid; yield 108.3 g (95.5%); mp 44.9–45.4°C (Lit. [15] mp 45–46°C); ESI-MS: *m/z* 151.95 ([M+H]$^+$); ^{1}H NMR ($CDCl_3$): δ 9.03 (s, 1H), 8.60 (s, 1H), 8.11 (s, 1H), 3.95 (s, 3H), 2.40 (s, 3H); FT-IR: 3417, 3055, 2957, 1721, 1579, 1439, 1384, 1320, 1296, 1219, 1110, 768 cm^{-1}.

5-Methyl-3-pyridinemethanol (3)

Sodium borohydride (4.4 g, 0.12 mol) was added to a suspension of 5-methylnicotinic acid methyl ester (5.0 g, 0.033 mol) in methanol (50 mL). The mixture was stirred for 1 h at 55°C, and then treated with water (5 mL) and concentrated under reduced pressure. The residue was extracted with ethyl acetate (2×50 mL). The extract was washed by brine, dried with anhydrous sodium sulfate, and filtered. The filtrate was concentrated under reduced pressure. The oily residue of **3** (4.2 g) was used directly in the next step.

5-Methyl-3-pyridinemethanol hydrobromide (4)

Hydrobromic acid (5 mL, 40%, 0.036 mol) was added dropwise to compound **3** (4.2 g) cooled in an ice bath. The mixture was then concentrated under reduced pressure, and the residue was treated with tetrahydrofuran/ethanol (1:1, 20 mL). The mixture was stirred for 30 min and the resultant white precipitate of **4** was filtered: yield 5.7 g, (84.6%); mp 126.8–128.4°C; MS: *m/z* 123.95 ([M-Br]$^+$); ^{1}H NMR (DMSO-d_6): δ 8.76 (1H, s), 8.70 (1H, s), 8.41 (1H, s), 4.69 (2H, s), 2.50 (3H, s); IR: 3312, 3172, 3028, 2687, 2064, 1623, 1557, 1442, 1405, 1330, 1059, 863, 681 cm^{-1}. Anal. Calcd for $C_7H_{10}BrNO$: C, 41.20; H, 4.94; Br, 39.16; N, 6.86. Found: C, 41.20; H, 4.94; Br, 39.12; N, 6.85.

3-(Bromomethyl)-5-methylpyridine bromide (5)

A mixture of compound **4** (5.0 g, 0.0245 mol), hydrobromic acid (50 mL, 40%, 0.34 mol), and xylene (25 mL) was heated under reflux with azeotropic removal of water with xylene. Xylene was evaporated under reduced pressure, and a residue was treated with acetone (45 mL). The mixture was sonicated for 1 h to wash out adsorbed impurities; then product **5** was filtered and dried: white solid; yield 5.2 g, (79.5%). mp 158.1158.8°C; MS: *m/z* 185.95 ([M-HBr]$^+$); ^{1}H NMR (DMSO-d_6): δ 8.84 (2H, s), 8.58 (1H, s), 4.88 (2H, s), 2.50 (3H, s); IR: 3225, 3110, 3014, 2964, 2924, 2553, 2036, 1556, 1462, 1344, 1317, 1229, 1030, 862, 736, 681 cm^{-1} [1].

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