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NOTE

Synthesis of 2-Amino-5-hydroxypyridine *via* Demethoxylation

J. CHENG* and C. LIU

Department of Chemical Engineering, Changzhou Institute of Engineering Technology, Changzhou 213164, P.R. China

*Corresponding author: Tel: +86 18118028001; E-mail: 4405313@qq.com

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A convenient and efficient four-step synthesis of 2-amino-5-hydroxypyridine can be achieved by protective reaction of 2-amino-5-bromopyridine in the presence of 2,5-hexanedione to yield 5-bromo-2-(2,5-dimethyl-1H-pyrrol-1yl)pyridine, methoxylation with sodium methylate to give 5-methoxy-2-(2,5-dimethyl-1H-pyrrol-1yl)pyridine, deprotective reaction with hydroxylamine hydrochloride to produce 2-amino-5-methoxypyridine and demethylation with 95 % H_2SO_4 to afford the title compound in an overall yield of 45 %.

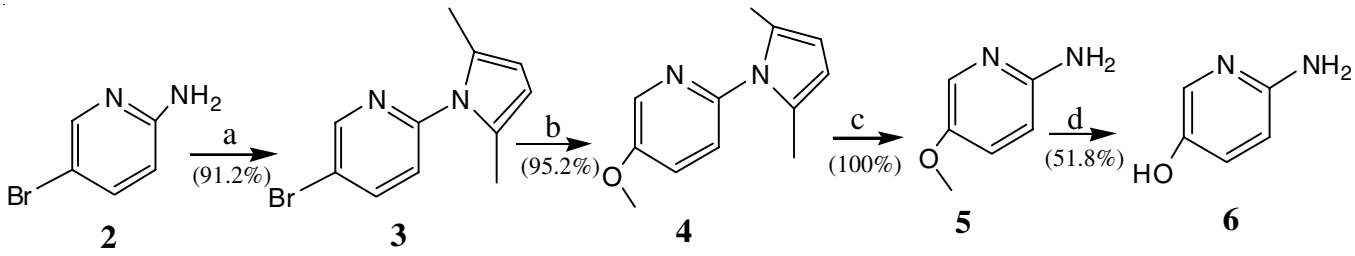
Keywords: Methoxylation, Demethylation, 2-Amino-5-methoxypyridine, 2-Amino-5-hydroxypyridine.

2-Amino-5-hydroxypyridine (**6**) is widely used in biological and pharmaceutical fields [1-5]. It is a key intermediate in the preparation of HIV inhibiting 9-hydroxy-6-(4-nitrophenyl)-pyrido[2′,1′:2,3]imidazo[4,5-c]isoquinolin-5(6H)-one [5]. Several syntheses of 2-amino-5-hydroxypyridine (**6**) have already been reported [5-8]. Most methods used 48 % HBr [5,6]. Also the start material 2-amino-5-iodopyridine is expensive [5,9]. A low-cost and clean demethylation technique is desirable. We report a convenient and efficient synthesis of 2-amino-5-hydroxypyridine (**6**) utilizing a low-cost and environmentally friendly reagent, 2-amino-5-bromo-pyridine (**2**) as start material and 95 % H_2SO_4 for the demethylation.

Reagents and solvents were obtained from commercial suppliers and were used without further purification. All melting points were determined on a XT34 binocular microscope (Beijing Tech Instrument Co., China) and were not corrected. NMR spectra were obtained on a Mercuryplus 400 spectrometer (^{1}H NMR at 400 Hz, ^{13}C NMR at 100 Hz) in $CDCl_3$ or DMSO-d_6 with tetramethylsilane as an internal standard; chemical shifts (δ) were reported in parts per million relative to tetramethylsilane. Chemical shifts were reported in ppm relative to the solvent resonance as the internal standard ($CDCl_3$, δ = 7.26 ppm). Analytical TLC and column chromatography were performed on silica gel GF254 and silica gel H60, respectively.

5-Bromo-2-(2,5-dimethyl-1H-pyrrol-1yl)pyridine (3): 2-Amino-5-bromopyridine (**2**) (10 mmol, 1.73 g), 2,5-hexanedione (12 mmol, 1.13 g) and *p*-toluene sulfonic acid (3 mmol, 0.52 g) was dissolved in toluene (30 mL) and heated to reflux in a Dean-Stark apparatus for 8-10 h until compound **2** can not be detected by TLC. After cooling to room temperature, the reaction mixture was washed with a saturated aqueous $NaHCO_3$ solution, water and brine. The organic phase was dried with $MgSO_4$ and concentrated in vacuum. The resulting orange liquid was dried under high vacuum and cooled to orange solid **3** (2.28 g, yield = 91.2 %), m.p. 67.6-68.9 °C (lit. [9] 69 °C); ^{1}H NMR (400 Hz, $CDCl_3$), δ (ppm): 2.130 (s, 6H, 2*CH_3), 5.905 (s, 2H, CH), 7.115-7.132 (d, 1H, pyr-H), 7.922-7.944 (dd, 1H, pyr-H), 8.651-8.656 (d, 1H, pyr-H); ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 13.19, 107.40, 118.91, 123.01, 128.59, 140.51, 150.41, 150.70.

5-Methoxy-2-(2,5-dimethyl-1H-pyrrol-1yl)pyridine (4): Sodium methoxide (40 mmol, 2.16 g) was dissolved in dry methanol (20 mL). DMF (20 mL), CuI (0.15 equiv., 2.5 mmol, 0.5 g) and **3** (8 mmol, 2.0 g) were added. The reaction mixture was heated to 80 °C for 3 h. After the mixture had been allowed to cool to room temperature, isopropylether and an aqueous NH_4Cl solution (5 %) were added, the mixture was stirred overnight. The solids were filtered off over Celite and the filtrate was extracted several times with dichloromethane. The combined organic phases were washed with a 10 % aqueous NH_4OH solution, dried with $MgSO_4$ and concentrated *in vacuo*. After drying in high *vacuo*, pure **4** (1.54 g, yield = 95.2 %) was obtained, m.p. 74.5-75.2 °C (lit. [10] 75 °C); ^{1}H NMR (400 Hz, $CDCl_3$), δ (ppm): 2.081 (s, 6H, 2*CH_3), 3.918 (s, OCH_3), 5.873 (s, 2H, CH), 7.146-7.163 (d, 1H, pyr-H), 7.312-7.336 (dd, 1H, pyr-H), 8.267-8.274 (d, 1H, pyr-H). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 12.99, 55.89, 106.31, 122.36, 128.70, 136.23, 145.01, 149.36, 154.74.



Scheme-I: Reagents: a: 1,4-hexanedione, *p*-TsOH; b: CH_3ONa, CuI; c: NH_2OHHCl; d: 95 % H_2SO_4

2-Amino-5-methoxy pyridine (5): A mixture of **4** (7 mmol, 1.41 g), hydroxylamine hydrochloride (45.5 mmol, 1.89 g), triethylamine (14 mmol, 1.41 g), ethanol (20 mL) and water (10 mL) was refluxed for 20 h. The solution was cooled and quenched with 2 M HCl, washed with isopropyl ether and the pH was adjusted to 9-10 with 6 M NaOH. The resulting mixture was extracted several times with diethyl ether. The combined organic phases were dried with $MgSO_4$ and the solvent was removed *in vacuo*. The oily residue was purified by column chromatography on silica gel (gradient elution: CH_2Cl_2/$CH_3COOC_2H_5$ = 1:3→ pure ethyl acetate) to give dark brown liquid 5 (0.87 g, yield = 100 %). ^{1}H NMR (400 Hz, $CDCl_3$), δ (ppm): 3.772 (s, 3H, OCH_3), 4.213 (br, 2H, NH_2), 6.493-6.462 (dd, 1H, pyr-H), 7.070-7.110 (dd, 1H, pyr-H), 7.766-7.775 (d, 1H, pyr-H). ^{13}C NMR (100 MHz, $CDCl_3$), δ (ppm): 56.28, 109.49, 125.73, 133.11, 148.60, 153.09.

2-Amino-5-hydroxy pyridine (6): 95 % H_2SO_4 (10 mL) was stirred at 80 °C, compound **5** (5 mmol, 0.62 g) was added dropwise to the stirred solution keeping the temperature at 80-85 °C. After the addition, stirring was continued at 90-93 °C for about 24 h until **5** can not be detected by TLC. The reaction mixture was poured into crash ice (100 g) and the solution was adjusted to pH 7-8 by gradual addition of Na_2CO_3. The resulting mixture was extracted several times with diethyl ether (**Scheme-I**). The combined organic phases were dried with anhydrous Na_2SO_4 and the solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel (gradient elution: CH_3OH/CH_2Cl_2 = 1:9) to give taupe solid **6** (0.29 g, yield = 51.8 %). ^{1}H NMR (400 Hz, DMSO-d_6), δ (ppm): 5.200 (br, 2H, NH_2), 6.327-6.350 (t, 1H, pyr-H), 6.893-6.923 (dd, 1H, pyr-H), 7.497-7.506 (dd, 1H, pyr-H), 8.636 (s, 1H, OH). ^{13}C NMR (100 MHz, DMSO-d_6), δ (ppm): 110.00, 128.16, 131.65, 145.25, 150.04.

Synthetic studies of the HIV inhibiting derivatives requires 2-amino-5-hydroxy pyridine (**6**) as a key intermediate and it was shown that the concise synthesis of its precursor, 2-amino-5-methoxy pyridine (**5**) using 2,5-hexanedione as protective agent, CH_3ONa as methoxylative agent and hydroxylamine hydrochloride as deprotective agent, proceeded in good yields. Meantime, the optimization of the synthetic conditions for demethylation of 2-amino-5-methoxy pyridine (**5**) using an environmentally friendly reagent (95 % H_2SO_4) and the methoxylation from a low-cost reagent (2-amino-5-bromo-pyridine **2**) were conducted.

Hydrobromic acid (48 %) is a fuming reagent, easily decomposed by oxygen in the air to Br_2, which is not environmentally friendly. Whenever possible, the clean reagents should be used. 95 % H_2SO_4 is a non-volatile and stable agent. Accordingly, 95 % H_2SO_4 was selected as a demethylating agent, which was found to be a cleaner agent and can raise the yield of 2-amino-5-hydroxy pyridine (**6**) to 51.8 %.

Previously used as start material for the synthesis of 5-methoxy-2-(2,5-dimethyl-1H-pyrrol-1yl)pyridine (**4**) is 2-amino-5-iodopyridine [10], which is expensive. It was found that using 2-amino-5-bromo pyridine (**2**) as starting material can also produce 5-methoxy-2-(2,5-dimethyl-1H-pyrrol-1yl)-pyridine (**4**) in good yield.

Conclusion

This synthetic route to 2-amino-5-hydroxypyridine (**6**) is an environmentally friendly and economical process, which is suitable for scaling up for use in the industrial production.

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