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Technical Notes

An Efficient and Cost-Effective Synthesis of 2-Phenyl-3-aminopyridine

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Abstract:

The synthesis of 2-phenyl-3-aminopyridine, a key intermediate in the preparation of 2-phenyl-3-aminopiperidine, from 2-chloro-3-aminopyridine is described using an imine as a protecting group for an aminopyridine. The in situ protection of 2-chloro-3-aminopyridine with benzaldehyde followed by Suzuki coupling with phenylboronic acid and subsequent acid hydrolysis provided the titled compound in a single, high-yielding step from inexpensive and commercially available starting materials.

Introduction

3-Amino-2-phenyl-piperidine is an important pharmacophore present in potent non-peptidic NK1 receptor antagonists[1−4] such as CP-99,994 and GR203040 (Figure 1) and has displayed utility as a chiral auxiliary for asymmetric epoxidations.[5]

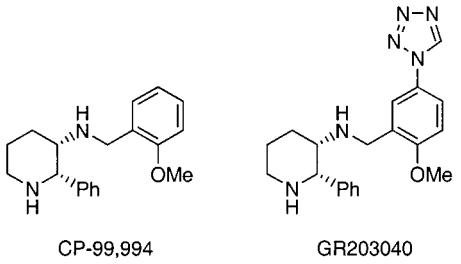


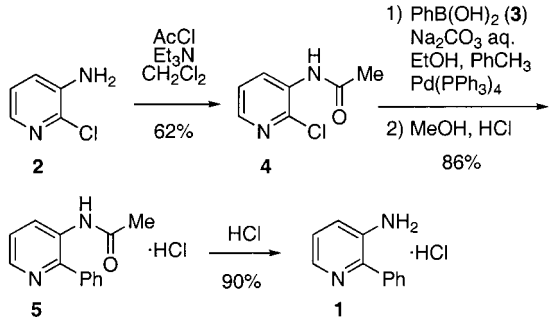
Figure 1.

Syntheses of the piperidine moiety have been reported starting from nitrobutyrate,[6] 2-chloro-3-nitropyridine,[7−9] as well as from 2-phenyl-3-aminopyridine (**1**).[10] The literature preparations of **1** included the low-yielding addition of phenyllithium to 3-aminopyridine[11] and alternatively a nickel-catalyzed coupling between a phenylzinc reagent and 2-chloro-3-aminopyridine (**2**).[12] Our work focused on a robust, cost-effective, and efficient synthesis of 2-phenyl-3-aminopyridine (**1**).

Discussion

Initial attempts at direct Suzuki coupling[13] between phenylboronic acid (**3**) and 2-chloro-3-aminopyridine (**2**) proved to be unproductive. However, if the aminopyridine was first protected as the acetamide (**4**),[14] then the palladium-mediated coupling proceeded efficiently with subsequent cleavage of **5** using HCl. While this synthesis was straightforward, the use of the acetamide as a protecting group resulted in a three-step process. However, it demonstrated that Suzuki coupling of **2** could be performed with a suitable protecting group on the aminopyridine (Scheme 1).

Scheme 1



The second protecting group considered was an imine. The preparation of the benzophenone imine was very slow (>3 days), whereas the reaction of 2-chloro-3-aminopyridine (**2**) with benzaldehyde (**6**) was accomplished in high yield overnight. The crude toluene solution was used directly for the Suzuki coupling under standard conditions with PhB(OH)$_2$ (**3**). The palladium-mediated coupling was very rapid and proceeded in less than 30 min. Following an extractive, acidic workup, a 90% yield of **1** was obtained (Scheme 2).

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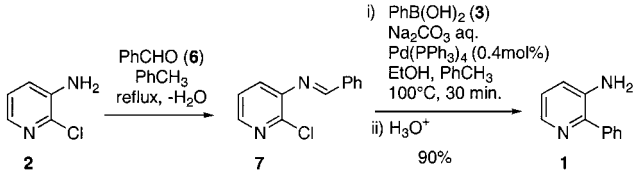
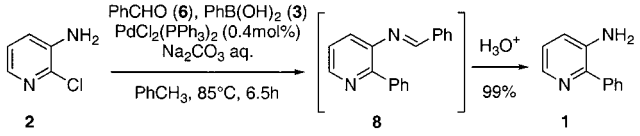
Scheme 2



Since the imine formation was fast, we speculated that the benzaldehyde imine (**7**) formation could be accomplished in situ under the cross-coupling conditions. Indeed, treatment of the **2** with benzaldehyde (**6**) (1.01 equiv), $PhB(OH)_2$ (**3**) (1.2 equiv), and $PdCl_2(PPh_3)_2$ (0.37 mol %) in a mixture of toluene and aqueous sodium carbonate (1.2 equiv) proved to be acceptable for production of the imine **7** (Scheme 3).

Scheme 3



Monitoring by HPLC confirmed that the reaction was complete within 7 h. At the end of the reaction, aqueous HCl was added to cleave imine **8** and to bring protonated **1** into the aqueous layer. After removal of the organic layer that contained benzaldehyde, the acidic layer was neutralized and extracted. The desired aniline was recovered from the organic extracts and isolated as a solid in 99% yield. [15]

Conclusions

Overall, we have developed a process for the one-pot synthesis of 2-phenyl-3-aminopyridine (**1**) that is operationally simple, high-yielding, robust, and amenable to multikilogram scale.

Experimental Section

General. Starting materials were obtained from commercial suppliers and used without further purification. Thin-layer chromatography was performed with EM Separations Technology silica gel F_{254}, HPLC was performed with a Hewlett-Packard Series 1100 using a Zorbax SB-CN column (4.6 × 25 mm) and 60/40 CH_3CN/pH 3.2 aqueous buffer mobile phase. Melting points were measured in open capillary tubes and are uncorrected. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were measured in $CDCl_3$ unless otherwise indicated.

***N*-(2-Chloro-pyridin-3-yl)-acetamide (4).** To a solution of 2-chloro-3-aminopyridine (**2**) (51.4 g, 400 mmol) in CH_2Cl_2 (800 mL) at 0 °C was added Et_3N (31.0 mL, 440 mmol) followed by AcCl (62.0 mL, 440 mmol). The reaction was allowed to warm to room temperature and was stirred overnight. The reaction mixture was poured into H_2O (800 mL), and the layers were separated. The organic layer was treated with Darco-G-60, heated to reflux, filtered over Celite, and concentrated to an oil. The oil was crystallized in iPr$_2$O, and the solids were filtered to afford 42.4 g (62% yield) of *N*-(2-chloro-pyridin-3-yl)-acetamide (**4**). Mp = 81−83 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23 (s, 3), 7.21 (dd, 1, J = 8.1, 4.7), 7.67 (bs, 1), 8.06 (dd, 1, J = 4.7, 1.3), 8.66 (d, 1, J = 7.9). ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.93, 123.34, 129.06, 131.89, 143.81, 144.08, 168.79. The melting point of **1** compared to the known data in the literature.[16]

***N*-(2-Phenyl-pyridin-3-yl)-acetamide Hydrochloride (5).** To a mixture of *N*-(2-chloro-pyridin-3-yl)-acetamide (**4**) (50,0 g, 29.3 mmol), $PhB(OH)_2$ (**3**) (39.3 g, 32.2 mmol), Na_2CO_3 (49.7 g, 46.9 mmol), in toluene (400 mL), EtOH (100 mL), and H_2O (200 mL) was added $Pd(PPh_3)_4$ (1.02 g, 0.883 mmol). The reaction mixture was heated to reflux for 8 h and cooled to room temperature, and the layers were separated. The aqueous layer was extracted with EtOAc (500 mL), and the organic extracts were combined and concentrated to a yellow solid. The crude solid was dissolved in MeOH (500 mL), and concentrated HCl was added (10 mL). The solution was concentrated to a low volume, and THF (500 mL) was added. The solid was triturated, filtered, and dried to afford *N*-(2-phenyl-pyridin-3-yl)-acetamide hydrochloride (**5**) (62.5 g, 86%). Mp = 262−263 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.52 (s, 3), 6.30 (bs, 2), 7.64−7.72 (m, 6), 7.78 (dd, 1, J = 1.2, 8.6), 8.06 (dd, 1, J = 1.2, 5.2).

2-Phenyl-3-aminopyridine Hydrochloride (1). To a solution of *N*-(2-phenyl-pyridin-3-yl)-acetamide hydrochloride (**5**) (61.9 g, 24.9 mmol) in THF (100 mL) was added concentrated HCl (100 mL). The reaction mixture was heated to reflux overnight and concentrated to a low volume. THF was added (2000 mL), and the volume was reduced to about 1000 mL as product started precipitating. The mixture was cooled to 0 °C and was granulated for 2 h. The solids were filtered to afford 2-phenyl-3-aminopyridine hydrochloride (**1**) (46.2 g, 90%). Mp = 226−227 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.35 (bs, 3), 7.61−7.74 (m, 6), 7.82 (dd, 1, J = 1.4, 8.6), 8.05 (dd, 1, J = 1.5, 5.4). Anal. Calcd for $C_{11}H_{11}ClN_2$: C, 63.93; H, 5.36; N, 13.55. Found: C,63.64; H, 5.20; N, 13.49.

2-Phenyl-3-aminopyridine (1). To 2-chloro-3-aminopyridine (**2**) (1.06 g, 8.24 mmol) in toluene (25 mL) was added benzaldehyde (**6**) (0.878 g, 8.27 mmol). The reaction mixture was stirred at reflux in a Dean−Stark apparatus until GC/MS analysis of the reaction mixture no longer showed starting material. The reaction mixture was cooled to room temperature, and the toluene solution containing benzylidene-(2-chloro-pyridin-3-yl)-amine (**7**) was added to a mixture of $PhB(OH)_2$ (**3**) (1.30 g, 10.7 mmol), Na_2CO_3 (2.66 g, 25.1 mmol), and $Pd(PPh_3)_4$ (47 mg, 0.38mol %) in water (10 mL). The reaction mixture was heated to 100 °C for 30 min, cooled to room temperature, and poured into 1 N aqueous NaOH (10 mL). The aqueous layer was removed, and the toluene layer was extracted with 1 N aqueous HCl (2 × 15 mL). The aqueous layer was neutralized to pH 12 with 6 N aqueous NaOH and extracted with MTBE (2 × 20 mL). The MTBE extracts were dried over $MgSO_4$, filtered, and concentrated to afford 2-phenyl-3-aminopyridine (**1**) as a solid which crystallized from iPr$_2$O (1.26 g, 90% yield). Mp

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= 67−68 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.88 (bs, 2), 7.02−7.11 (m, 2). 7.28−7.53 (m, 3), 7.67−7.71 (m, 2), 8.13−8.16 (m, 1). ^{13}C NMR (100 MHz, $CDCl_3$) δ 122.57, 122.96, 128.14, 128.38, 128.72, 138.54, 139.86, 139.93, 144.93. The melting point of **1** compared to the known data in the literature.[11]

2-Phenyl-3-aminopyridine (1). In a 5L flask was added toluene (1.5L), 2-chloro-3-aminopyridine (**2**) (100 g, 0.778 mol), $PhB(OH)_2$ (**3**) (114 g, 0.934 mol), and benzaldehyde (**6**) (83.4 g, 0.786 mol). The mixture was stirred at room temperature for 10 min, and *trans*-dichloro(triphenylphosphine)palladium (II) (2.0 g, 2.8 mmol) was added. The mixture was stirred for 15 min, and a solution of Na_2CO_3 (99.0 g, 0.934 mol) in water (1.5 L) was added. The biphasic mixture was heated to reflux followed by HPLC. After 6.5 h, the mixture was cooled to room temperature, and Celite (2.0 g) was added.. The suspension was filtered, and the layers were allowed to separate. The organic layer was treated with 3 N HCl (540 mL). The organic layer containing the benzaldehyde (**6**) was discarded, and the aqueous acidic layer was diluted with MTBE (500 mL) and the pH adjusted to about 12 with 50% aqueous NaOH. The organic layer was concentrated to an oil which crystallized upon standing and afforded 2-pheyl-3-aminopyridine (**1**) (130.4 g, 99%) having spectroscopic data identical to the procedure described above.

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