Preparation of 2-, 4-, 5-, and 6-Aminonicotinic Acid *tert*-Butyl Esters

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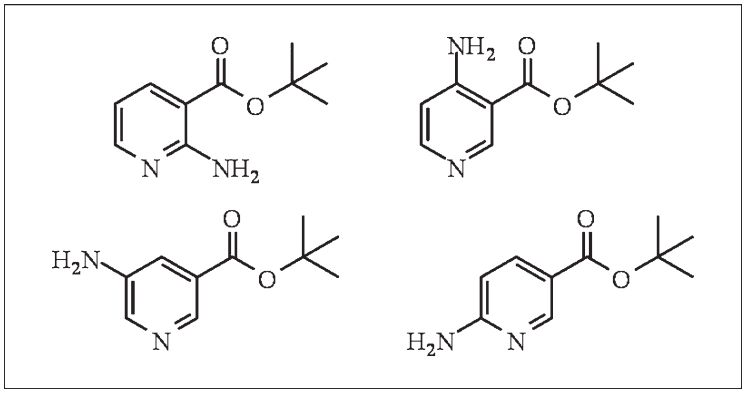

Procedures are reported to prepare the *tert*-butyl esters of 2-aminonicotinic acid, 4-aminonicotinic acid, 5-aminonicotinic acid, and 6-aminonicotinic acid from 2-chloronicotinic acid, 4-chloronicotinic acid, 5-bromonicotinic acid, and 6-chloronicotinic acid, respectively, without need for purification of intermediates.

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INTRODUCTION

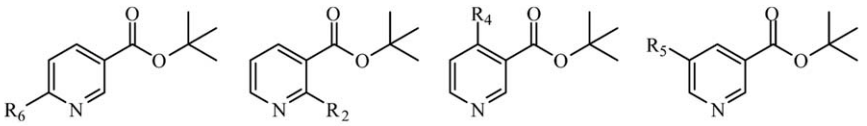
Aminonicotinic acids are useful intermediates for the synthesis of numerous compounds of biological interest. Compounds containing the 2-amino [1], 4-amino [2], 5-amino [3], and 6-aminonicotinic acid [4] moieties appear frequently in medicinal chemistry programs.

Recently, we required access to a series of derivatives of 6-aminonicotinic acid [5]. To facilitate the synthesis of our target compounds, we sought to use *tert*-butyl 6-aminonicotinate (**1a**) as an intermediate, which would permit us to use a global deprotection strategy at the last step of synthesis under acidic conditions, which would be compatible with parallel synthesis techniques. A search of the literature returned two references to this substance [6]; however, the preparation of **1a** was not described in these references in even the most general terms. We, therefore, sought to develop a convenient and scaleable synthesis of this intermediate.

Experimentation with 6-aminonicotinic acid revealed that direct preparation of the *tert*-butyl ester was problematic. Unlike 6-aminonicotinic acid benzyl ester, which may be prepared by direct alkylation of 6-aminonicotinic acid with benzyl bromide [5,7], esterification of 6-aminonicotinic acid mediated by carbodiimides [8] or thionyl chloride [9] failed to return detectable amounts of **1a**. Esterification of 6-aminonicotinic acid using isobutylene and an acid catalyst was likewise unsuccessful. In these reactions, the low solubility of 6-aminonicotinic acid in reaction–compatible solvents was at least partially responsible for the difficulties encountered.

We then turned our attention to the route shown in Scheme 1, in which the *tert*-butyl ester is prepared first, after which the amino group is introduced. 6-Chloronicotinic acid *tert*-butyl ester (**2a**) was prepared in 97% yield from the acid and di-*tert*-butyl dicarbonate in the presence of (4-dimethylamino)pyridine [10]. Subsequent aminolysis with ammonia proved to be inefficient [11]; however, aminolysis with hydrazine hydrate proceeded readily to afford the hydrazine **3a** in 79% yield. Reductive cleavage of the hydrazine to the amine was accomplished with Raney® nickel in 78% yield [12]. Gratifyingly, no purification of the intermediates was required and **1a** was isolated in 60% yield over three steps.

Following this, we sought to prepare the 2-amino (**1b**), 4-amino (**1c**), and 5-amino (**1d**) nicotinic acid *tert*-butyl esters. The preparation of **1b** and **1c** were accomplished using the same procedure as used for the preparation of **1a**, to afford the previously unreported *tert*-butyl esters.



	R_6	Yield		R_2	Yield		R_4	Yield		R_5	Yield
1a	NH_2	97	**1b**	NH_2	84	**1c**	NH_2	82	**1d**	NH_2	85
2a	Cl	79	**2b**	Cl	92	**2c**	Cl	67	**2d**	Br	96
3a	$NHNH_2$	78	**3b**	$NHNH_2$	92	**3c**	$NHNH_2$	96			

Not surprisingly, the preparation of **1d** required a different route, in as much as the S_NAr reaction used to prepare **1a–c** was not feasible in this case (Scheme 2). However, copper-catalyzed amination of *tert*-butyl 5-bromonicotinate (**2d**) with ammonium hydroxide in the absence of potassium carbonate proceeded smoothly to afford **1d** in 82% yield over two steps [13].

In summary, we have developed convenient, scaleable procedures to prepare the *tert*-butyl esters of 2-aminonicotinic acid, 4-aminonicotinic acid, 5-aminonicotinic acid, and 6-aminonicotinic acid from readily available starting materials without need for purification of intermediates.

EXPERIMENTAL

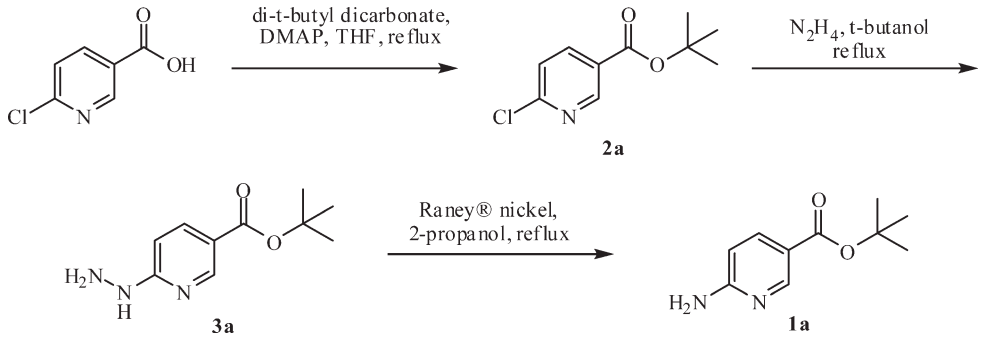
All solutions were dried over anhydrous magnesium sulfate unless otherwise noted. All evaporations were carried out on a rotary evaporator at about 30 Torr. Commercial reagents were used as received without additional purification. Solvents were commercial anhydrous grades and were used without further drying. Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded on a 400 MHz spectrometer. Mass-spectral data were recorded using atmospheric pressure chemical ionization or on a gas chromatograph fitted with a mass-selective detector using electron impact ionization. Infrared spectra were recorded as neat films on a FTIR.

General procedure for preparation of *tert*-butyl halonicotinate esters. ***tert-Butyl 6-chloronicotinate (2a).*** 6-Chloronicotinic acid (3.16 g, 20 mmol) and (4-dimethylamino)pyridine (208 mg, 1.7 mmol) were dissolved in 20 mL of tetrahydrofuran. The mixture was heated under reflux while a solution of di-*tert*-butyl dicarbonate (10.79 g, 49.4 mmol) in 20 mL of tetrahydrofuran was added dropwise from addition funnel over 30 min. Heating under reflux was continued for 4 h, and then the mixture was allowed to stand at 20°C overnight. The mixture was concentrated, and the residue was partitioned between methyl *tert* -butyl ether and water. The phases were separated and the organic phase was washed again with water, then with 1*M* phosphoric acid, water, twice with 10% sodium carbonate, and brine. The solution was dried and concentrated to afford 4.28 g (97%) of **2a** as an oil that soon solidified, m.p. 53–55°C (reported m.p. 53–54°C [14]) IR 2980, 1708 cm^{-1}. ^1H NMR (deuteriochloroform): δ 1.61 (s, 9 H), 7.39 (d, J = 7.8 Hz, 1 H), 8.19 (dd, J = 8.4, 2.3 Hz, 1 H), 8.94 (d, J = 2.0 Hz, 1 H). ^{13}C NMR (deuteriochloroform): δ 27.81, 28.03, 82.45, 123.84, 126.62, 139.39, 151.02, 155.02, 163.38. ms: *m/z* 214, 216 ($M+H^+$, Cl isotope pattern).

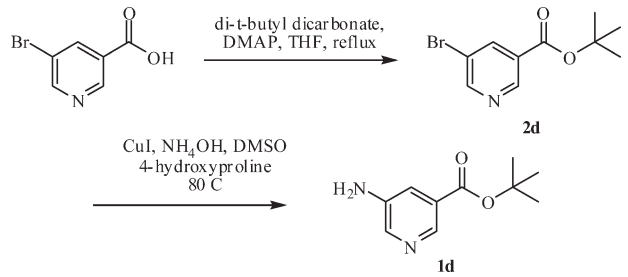
Anal. Calcd for $C_{10}H_{12}ClNO_2$: C, 56.21; H, 5.66; N, 6.56; Cl, 16.59. Found: C, 56.20; H, 5.52; N, 6.46; Cl, 16.66.

tert-Butyl 2-chloronicotinate (2b). This compound was prepared in a similar manner from 2-chloronicotinic acid (3.19 g, 20.3 mmol), (4-dimethylamino)pyridine (205 mg, 1.7 mmol), and di-*tert*-butyl dicarbonate (10.83 g, 49.6 mmol) in 40 mL of tetrahydrofuran. It was obtained as colorless oil, 4.33 g (92%). IR 2980, 1726 cm^{-1}. ^1H NMR (deuteriochloroform): δ 1.61 (s, 9 H), 7.39 (d, J = 7.8 Hz, 1 H), 8.19 (dd, J = 8.4, 2.3

Scheme 1



Scheme 2



Hz, 1 H), 8.94 (d, J = 2.0 Hz, 1 H); ^{13}C NMR (deuteriochloroform): δ 27.87, 28.06, 83.36, 122.03, 139.74, 149.47, 151.21, 163.91. ms: *m/z* 214, 216 (M+H$^+$, Cl isotope pattern).

Anal. Calcd for $C_{10}H_{12}ClNO_2$: C, 56.21; H, 5.66; N, 6.56; Cl, 16.59. Found: C, 56.21; H, 5.33; N, 6.33; Cl, 16.55.

tert-Butyl 4-chloronicotinate (2c). This compound was prepared in a similar manner from 4-chloronicotinic acid (3.11 g, 19.7 mmol), (4-dimethylamino)pyridine (189 mg, 1.6 mmol), and di-*tert*-butyl dicarbonate (10.91 g, 49.9 mmol) in 40 mL of tetrahydrofuran. It was obtained as colorless oil that quickly solidified, 2.83 g (67%), m.p. 37–39°C (decomposes) [15]. IR 2979, 1725 cm^{-1}. ^{1}H NMR (deuteriochloroform): δ 1.63 (s, 9 H) 7.39 (d, J = 5.46 Hz, 1 H) 8.55 (d, J = 5.27 Hz, 1 H) 8.96 (s, 1 H); ^{13}C NMR (deuteriochloroform): δ 28.15, 83.50, 125.84, 143.89, 151.70, 151.75, 162.97. ms: *m/z* 214, 216 (M+H$^+$, Cl isotope pattern).

Anal. Calcd for $C_{10}H_{12}ClNO_2$: C, 56.21; H, 5.66; N, 6.56; Cl, 16.59. Found: C, 55.30; H, 5.89; N, 6.45; Cl, 16.45.

tert-Butyl 5-bromonicotinate (2d). This compound was prepared in a similar manner from 5-bromoonicotinic acid (4.05 g, 20.1 mmol), (4-dimethylamino)pyridine (202 mg, 1.6 mmol), and di-*tert*-butyl dicarbonate (10.98 g, 50.3 mmol) in 40 mL of tetrahydrofuran. It was obtained as colorless oil that quickly solidified, 5.81 g (96%), m.p. 54–56°C. IR 2978, 1717 cm^{-1}. ^{1}H NMR (deuteriochloroform): δ 1.61 (s, 9 H) 8.36 (t, J = 2.05 Hz, 1 H) 8.81 (d, J = 2.15 Hz, 1 H) 9.07 (d, J = 1.95 Hz, 1 H); ^{13}C NMR (deuteriochloroform): δ 28.06, 82.76, 120.41, 129.02, 139.32, 148.79, 153.95, 162.98. ms: *m/z* 258, 260 (M+H$^+$, Br isotope pattern).

Anal. Calcd for $C_{10}H_{12}BrNO_2$: C, 46.53; H, 4.69; N, 5.43; Br, 30.96. Found: C, 46.52; H, 4.65; N, 5.33; Br 31.26.

General procedure for reaction of *tert*-butyl chloronicotinate esters with hydrazine hydrate. ***tert-Butyl 6-hydrazinylnicotinate (3a).*** Compound **2a** (2.13 g, 10 mmol) was dissolved in 40 mL of *tert*-butanol with heating under reflux. After all **2a** had dissolved, hydrazine hydrate (4.8 mL, 99 mmol) was added in one portion. Heating was continued while the reaction was monitored by TLC on aliquots that had been removed and quenched into water and methyl *tert*-butyl ether. After 3 h, **2a** had been consumed by TLC analysis. The mixture was cooled and concentrated. The residue was diluted with methyl *tert*-butyl ether and washed with water (four times), then with brine, and dried. Concentration afforded a viscous colorless syrup that solidified on standing, 1.65 g (79%), m.p. 95–97°C. IR 3310, 2975, 1694, 1597 cm^{-1}. ^{1}H NMR (methanol-d_4): δ 1.58 (s, 9 H) 6.78 (d, J = 8.78 Hz, 1 H) 7.94 (d, J = 8.78 Hz, 1 H) 8.58 (br. s., 1 H); ^{13}C NMR (methanol-d_4): δ 28.67, 82.03, 107.06, 118.20, 139.28, 151.49, 164.81, 166.89. ms: *m/z* 210 (M+H$^+$).

Anal. Calcd for $C_{10}H_{15}N_3O_2$: C, 57.40; H, 7.23; N, 20.08. Found: C, 57.22; H, 7.36; N, 19.71.

tert-Butyl 2-hydrazinylnicotinate (3b). This compound was prepared in a similar manner from **2b** (4.00 g, 18.7 mmol) and hydrazine hydrate (9 mL, 200 mmol) in 75 mL of *tert*-butanol. It was obtained as a yellow solid, 3.61 g (92%), m.p. 71–73°C. IR 3394, 2976, 1684 cm^{-1}. ^{1}H NMR (methanol-d_4): δ 1.60 (s, 9 H) 6.68 (dd, J = 7.80, 4.88 Hz, 1 H) 8.13 (dd, J = 7.71, 1.85 Hz, 1 H) 8.30 (dd, J = 4.88, 1.76 Hz, 1 H); ^{13}C NMR (methanol-d_4): δ 27.23, 81.76, 108.04, 112.00, 140.25, 152.38, 159.97, 166.32. ms: *m/z* 210 (M+H$^+$).

Anal. Calcd for $C_{10}H_{15}N_3O_2$: C, 57.40; H, 7.23; N, 20.08. Found: C, 57.27; H, 7.29; N, 19.81.

tert-Butyl 4-hydrazinylnicotinate (3c). This compound was prepared in a similar manner from **2c** (2.83 g, 13.2 mmol) and hydrazine hydrate (7 mL, 130 mmol) in 50 mL of *tert*-butanol. It was obtained as viscous yellow syrup, 2.77 g (96%). IR 3338, 2977, 1679 cm^{-1}. ^{1}H NMR (methanol-d_4): δ 1.49–1.81 (s, 9 H) 7.26 (dd, J = 6.24, 0.59 Hz, 1 H) 8.13 (d, J = 6.24 Hz, 1 H) 8.63 (s, 1 H); ^{13}C NMR (methanol-d_4): δ 28.63, 83.07, 107.38, 108.65, 152.06, 152.67, 159.00, 168.22. ms: *m/z* 210 (M+H$^+$).

The tosylate salt was prepared from 124 mg of **3c** and 100 mg *p*-toluenesulfonic acid monohydrate in 2 mL of ethyl acetate, m.p. 142–143°C (decomposes).

Anal. Calcd for $C_{10}H_{15}N_3O_2 \cdot C_7H_8O_3S$: C, 53.53; H, 6.08; N, 11.02. Found: C, 53.49; H, 6.18; N, 10.77.

General procedure for reduction of *tert*-butyl hydrazinonicotinate esters with Raney nickel. ***tert-Butyl 6-aminonicotinate (1a).*** Compound **3a** (1.65 g, 7.9 mmol) was dissolved in 25 mL of 2-propanol with heating under reflux. The mixture was stirred vigorously while Raney nickel 2400 active catalyst suspension (8 mL, 50% in water) was added at a rate slow enough to control gas evolution. Heating was continued while the reaction was monitored by TLC on aliquots that had been removed and quenched into water and methyl *tert* -butyl ether. After 1 h, **3a** had been consumed by tlc analysis. The mixture was cooled and concentrated. The residue was diluted with methyl *tert*-butyl ether and washed with water, dilute sodium hydroxide, water, brine, and dried. Concentration afforded viscous tan syrup that solidified on standing. This was recrystallized from toluene, washed with pentane, and dried under vacuum to yield 1.19 g (78%) of **1a** as a white solid, m.p. 94–96°C. IR 3362, 3201, 1692, 1603 cm^{-1}. ^{1}H NMR (deuteriochloroform): δ 1.58 (s, 9 H), 4.85 (br. s., 2 H), 6.46 (d, J = 8.6 Hz, 1 H), 7.97 (dd, J = 8.6, 2.1 Hz, 1 H), 8.68 (d, J = 2.0 Hz, 1 H); ^{13}C NMR (deuteriochloroform): δ 28.20, 80.65, 107.17, 117.84, 138.69, 151.07, 160.92, 164.98. ms: *m/z* 195 (M+H$^+$).

Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.84; H, 7.27; N, 14.42. Found: C, 61.93; H, 7.24; N, 14.26.

tert-Butyl 2-aminonicotinate (1b). This compound was prepared in a similar manner from **3b** (3.61 g, 17.2 mmol) and Raney nickel 2400 active catalyst suspension (6 mL, 50% in water) in 100 mL of 2-propanol. It was obtained as a white solid, 2.81 g (84%), m.p. 117–118°C. IR 3431, 1684, 1616 cm^{-1}. ^{1}H NMR (deuteriochloroform): δ 1.58 (s, 9 H) 6.44 (br. s., 2 H) 6.59 (dd, J = 7.82, 4.89 Hz, 1 H) 8.06 (dd, J = 7.82, 1.95 Hz, 1 H) 8.18 (dd, J = 4.89, 1.95 Hz, 1 H); ^{13}C NMR (deuteriochloroform): δ 28.21, 81.39, 107.89, 112.52, 140.16, 153.00, 159.47, 166.37. ms: *m/z* 195 (M+H$^+$).

Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.84; H, 7.27; N, 14.42. Found: C, 61.94; H, 7.45; N, 14.34.

tert-Butyl 4-aminonicotinate (1c). This compound was prepared in a similar manner from **3c** (2.54 g, 12.1 mmol) and Raney nickel 2400 active catalyst suspension (6 mL, 50% in water) in 40 mL of 2-propanol. It was obtained as a white solid, 1.93 g (82%), m.p. 129–131°C. IR 3409, 1689, 1621 cm^{-1}. ^1H NMR (deuteriochloroform): δ 1.59 (s, 9 H) 6.20 (br. S, 2 H) 6.48 (d, $J = 5.85$ Hz, 1 H) 8.16 (d, $J = 5.85$ Hz, 1 H) 8.84 (s, 1 H).; ^{13}C NMR (deuteriochloroform): δ 28.23, 81.51, 109.10, 110.63, 151.77, 153.25, 154.91, 166.95. ms: *m/z* 195 ($M+H^+$).

Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.84; H, 7.27; N, 14.42. Found: C, 61.91; H, 7.44; N, 14.32.

tert-Butyl 5-aminonicotinate (1d). Cuprous iodide (438 mg, 2.3 mmol), *trans*-4-hydroxy-L-proline (590 mg, 4.5 mmol), and **2d** (2.89 g, 11.2 mmol) were stirred with 20 mL of dimethyl sulfoxide in a screw cap pressure tube. Concentrated ammonium hydroxide (12 mL, 180 mmol) was added, and the tube was closed and the homogeneous blue solution was heated at 80°C overnight. The mixture was then cooled, diluted with 100 mL of saturated ammonium chloride solution and extracted with 30 mL of 1,1,1-trichloroethane [16]. The aqueous phase was separated and extracted with another 30 mL portion of 1,1,1-trichloroethane. The combined extracts were dried and concentrated to afford 1.85 g (85%) of **1d** as a white solid, m.p. 107–108°C. IR 3370, 3208, 2978, 1704 cm^{-1}. ^1H NMR (deuteriochloroform): δ 1.59 (s, 9 H) 3.82 (br. s., 2 H) 7.51 (dd, $J = 2.93$, 1.76 Hz, 1 H) 8.21 (d, $J = 2.73$ Hz, 1 H) 8.57 (d, $J = 1.76$ Hz, 1 H); ^{13}C NMR (deuteriochloroform): δ 28.14, 81.73, 121.72, 127.88, 140.49, 140.99, 142.09, 164.75. ms: *m/z* 195 ($M+H^+$).

Anal. Calcd for $C_{10}H_{14}N_2O_2$: C, 61.84; H, 7.27; N, 14.42. Found: N, 61.59; H, 7.15, N, 14.21.

Telescoped large-scale preparation of 1a. A mixture of 6-chloronicotinic acid (50 g, 0.32 mol) and (4-dimethylamino)-pyridine (3.3 g, 0.027 mol) in 150 mL of anhydrous tetrahydrofuran was stirred and heated to reflux, while a solution of di-*tert*-butyl dicarbonate (172 g, 0.79 mol) in 150 mL of dry tetrahydrofuran was added dropwise from an addition funnel over 1.5 h. The resulting mixture was heated at reflux for an additional 2 h and then cooled to room temperature. The reaction mixture was concentrated and partitioned between methyl *t*-butyl ether (500 mL) and water (500 mL). The layers were separated, and the organic layer was washed with water, saturated ammonium chloride solution (200 mL), and brine and dried. Concentration afforded crude **2a** (95 g) as a yellow solid, which was used for the next step without further purification.

To a solution of **2a** (95 g, 0.32 mol) in *tert*-butanol (100 mL) was added hydrazine hydrate (186 g, 180 mL, 3.2 mol) dropwise from addition funnel with stirring. Heating was continued while the reaction was monitored by TLC on aliquots that had been removed and quenched into water and methyl *tert*-butyl ether. After 3 h, **2a** had been consumed by TLC analysis. The mixture was cooled and concentrated, then diluted with methyl *tert*-butyl ether (200 mL) and washed with water, saturated ammonium chloride, and dried. Concentration afforded **3a** (78 g) as a white solid, which was used for the next step without further purification.

A solution of **3a** (29.5 g, 0.14 mol) and Raney nickel 2400 active catalyst suspension (about 20 mL) in 300 mL of methanol was hydrogenated under 50 psi of hydrogen at room temperature for 24 h in a 500-mL Parr reaction bottle. The reaction mixture was filtered through Celite and concentrated. The residue was diluted with petroleum ether, filtered, dried over anhydrous sodium sulfate, and concentrated to give 19.9 g (73%) of **1a** as a light yellow solid (purity 97.87% by HPLC).

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[11] Aminolysis of **2** by ammonia with or without catalysis by copper afforded **1** in yields of <10%.

The reduction could be carried out with or without an additional reducing agent, such as hydrogen or hydrazine hydrate, being present. In addition, the latter two may be telescoped into a one pot procedure on large scale.

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