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Zwitterion Formation and Subsequent Carboxylate-Pyridinium NH Synthon Generation through Isomerization of 2-Anilinonicotinic Acid

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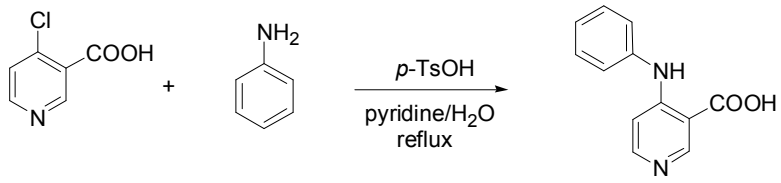
1. Synthesis

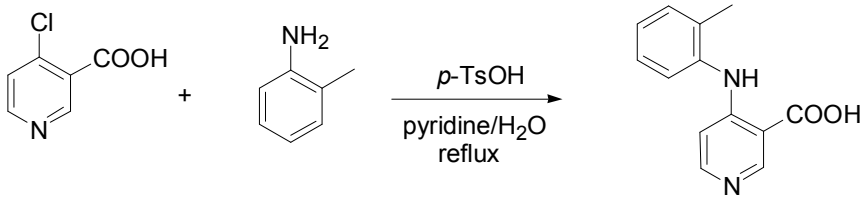
1) Synthesis of 4-phenylamino-nicotinic acid (**1**)



4-Chloronicotinic acid (1.0g, 6.37 mmol) and aniline (0.59 g, 6.37 mmol) were suspended in pyridine (0.5 g, 6.37mmol), *p*-TsOH (0.6 g, 6.37 mmol) in 18 mL of water and 10mL acetone was added to the mixture. The reaction was raised to 75 ° C. The resulting system was refluxed overnight and then it was cooled to room temperature. The solid precipitated from the reaction mixture was purified by recrystallization. The product was obtained as white solid (0.91g, yield%: 67).

^{1}H NMR (400 MHz, D_2O)：δppm 8.70 (s, 1H), 7.84 (s, 1H), 7.37 (s, 2H), 7.28 (s, 1H), 7.19 (d, J = 7.1 Hz, 2H), 6.89 (s, 1H); ^{13}C NMR (151 MHz, D_2O)：δppm 167.56, 157.10, 144.77, 143.48, 140.90, 139.61, 135.70, 130.63, 129.55, 128.61, 127.60, 126.36, 124.99, 109.47, 109.03, 108.41; IR (KBr, cm^{-1}): 3435 (m), 3058 (s), 2938 (s)，1643 (s),1508 (s), 1330 (m), 1265 (s), 1216 (s), 1159 (s), 818 (s), 746 (s), 676 (s), 561 (s), 526 (s); MS (ESI): 215.66 (M+1); mp: 285° C.

2) Synthesis of 4-o-Tolylamino-nicotinic acid (**2**)

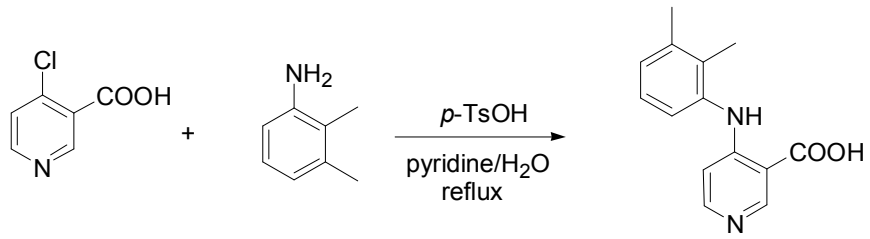


4-Chloronicotinic acid (1.51g, 9.52mmol) and o-toluidine (1.02g, 9.52 mmol) were suspended in pyridine (0.75g, 9.52mmol), *p*-TsOH (0.9g, 4.76 mmol) in 18mL of water was added to the mixture. The reaction was raised to 105 ° C. The resulting system was refluxed overnight and then it was cooled to room temperature. The solid precipitated from the reaction mixture was purified by trituration in EtOAc (1.52g, yield%: 70).

^{1}H NMR (400 MHz, D_2O): δppm 8.32 (s, 1H), 7.42 (s, 1H), 6.61 (d, J = 8.7 Hz, 2H), 6.41 (d, J = 8.4 Hz, 2H), 6.19 (d, J = 6.5 Hz, 1H), 3.36 (s, 3H).; ^{13}C NMR (151 MHz,

D_2O)：δppm 173.98, 155.66, 153.08, 152.12, 150.95, 150.31, 149.13, 131.63, 125.54, 124.28, 114.98, 113.92, 106.98, 106.00, 55.77, 54.95; IR (KBr, cm^{-1}): 3421.51 (s), 2474.09 (s), 1962.35 (s), 1646.17 (s), 1552.02 (s), 1513.46 (s), 1354.46 (s), 1310.26 (s), 1269.58 (s), 1220.83 (s), 1163.15 (s), 1039.99 (s), 820.27 (s), 766.22 (s), 680.48 (s), 651.11 (s) ; MS (ESI): 229.46 (M+1); mp: 274º C.

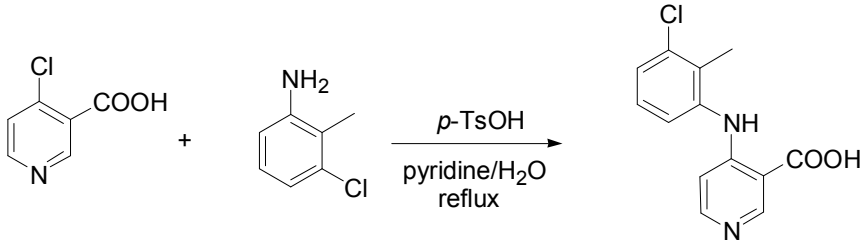
3) Synthesis of 4-(2,3-Dimethyl-phenylamino)-nicotinic acid (**3**)



4-Chloronicotinic acid (0.3 g, 1.9 mmol) and 2,3-dimethylaniline (0.23 g, 1.9 mmol) were suspended in pyridine (0.15 g, 1.9 mmol), *p*-TsOH (0.18 g, 0.95 mmol) in 8 mL of water and 2mL acetone was added to the mixture. The reaction was raised to 75 ° C. The resulting system was refluxed overnight and then it was cooled to room temperature. The solid precipitated from the reaction mixture was purified by trituration in EtOAc (0.35g, yield%: 78).

^{1}H NMR (400 MHz, D_2O): δppm 8.29 (s, 1H), 7.19 (d, J = 6.8 Hz, 1H), 6.41 (d, J = 28.4 Hz, 3H), 5.81 (d, J = 5.5 Hz, 1H), 1.66 (s, 3H), 1.54 (s, 3H); ^{13}C NMR (151 MHz, D_2O)：δppm 174.04, 152.22, 150.05, 138.22, 136.79, 131.75, 126.09, 124.77, 122.49, 114.00, 107.17, 20.08, 19.33, 13.50, 12.66.; IR (KBr, cm^{-1}): 3208.20 (m), 2420.28 (m), 1640.88 (s), 1550.14 (s), 1464.04 (s), 1362.68 (s), 1263.90 (s), 1221.50 (s), 1156.31 (s), 1066.73 (s), 1019.67 (s), 820.40 (s), 794.90 (s), 698.11 (s), 680.21 (s), 634.23 (s); MS (ESI): 243.37 (M+1); mp: 284º C.

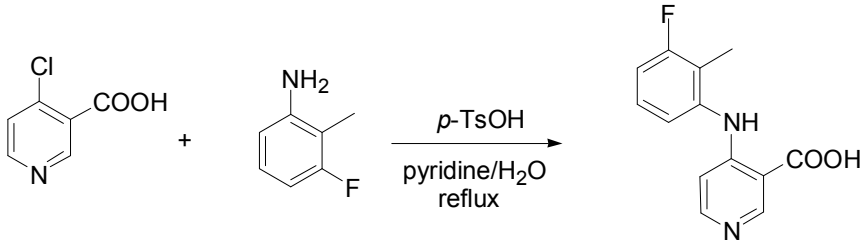
4) Synthesis of 4-(3-Chloro-2-methyl-phenylamino)-nicotinic acid (**4**)



4-Chloronicotinic acid (0.3 g, 1.9 mmol) and 2,3-dimethylaniline (0.23 g, 1.9 mmol) were suspended in pyridine (0.15 g, 1.9 mmol), *p*-TsOH (0.18 g, 0.95 mmol) in 8 mL of water and 2mL acetone was added to the mixture. The reaction was raised to 75 ° C. The resulting system was refluxed overnight and then it was cooled to room temperature. The solid precipitated from the reaction mixture was purified by trituration in EtOAc (0.21g, yield%: 60).

^{1}H NMR (400 MHz, D_2O)：δppm 8.32 (s, 1H), 7.42 (s, 1H), 6.61 (d, *J* = 8.7 Hz, 2H), 6.41 (d, *J* = 8.4 Hz, 2H), 6.19 (d, *J* = 6.5 Hz, 1H), 3.36 (s, 3H); ^{13}C NMR (151 MHz, D_2O)：δppm 173.77, 152.45, 150.29, 149.15, 138.43, 131.22, 127.33, 126.24, 125.45, 123.16, 114.33, 107.39, 107.39, 61.73 – 61.60, 14.69, 13.84; IR (KBr, cm^{-1}): 3202.47 (s), 2638.80 (m), 1642.19 (s), 1528.86 (s), 1449.54 (s), 1375.41 (s), 1282.98 (s), 1231.06 (s), 1174.84 (s), 1018.53 (s), 917.28 (s), 812.97 (s), 769.13 (s), 708.84 (s), 678.75 (s), 610.08 (s); MS (ESI): 263.89 (M+1); mp: 276^o C.

5) Synthesis of 4-(3-Fluoro-2-methyl-phenylamino)-nicotinic acid (**5**)

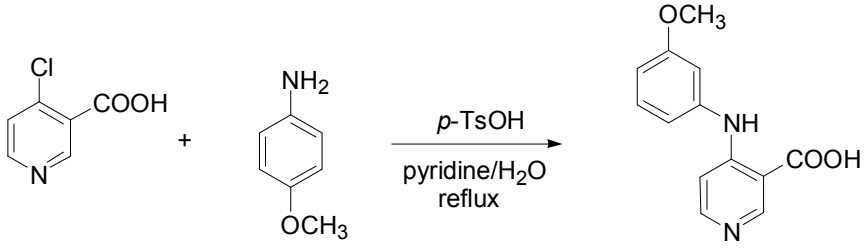


4-Chloronicotinic acid (0.219 g, 1.23 mmol) and 3-fluoro-2-methylaniline (0.153 g, 1.23 mmol) were suspended in pyridine (0.11 g, 1.23 mmol), *p*-TsOH (0.12 g, 0.615 mmol) in 10 mL of water was added to the mixture. The reaction was raised to 105 ° C. The resulting system was refluxed overnight and then it was cooled to room temperature. The solid precipitated from the reaction mixture was purified by trituration in EtOAc (0.11g, yield%: 37).

^{1}H NMR(600 MHz, D_2O)：δ 8.64 (s, 1H), 7.45 (s, 1H), 6.96 (d, *J* = 34.8 Hz, 1H), 6.84 (s, 1H), 6.70 (s, 1H), 6.40 (s, 1H), 1.92 (s, 3H); ^{13}C NMR：(151 MHz, D_2O)：δ 173.9, 161.4, 152.3, 151.1, 149.8, 138.8, 126.3, 119.3, 118.3, 114.5, 110.0, 107.1, 8.71; IR (KBr, cm^{-1}): 3088.04 (m), 2473.73 (m), 1702.87 (s), 1647.33 (s), 1552.40 (s), 1518.63 (s), 1466.68 (s), 1349.04 (s), 1301.04 (s), 1222.83 (s), 1176.73 (s), 1148.83

(s), 819.22 (s), 787.43 (s), 751.01 (s), 680.33 (s); MS (ESI): 247.50 (M+1); mp: 243 °C.

6) Synthesis of 4-(4-Methoxy-phenylamino)-nicotinic acid (**6**)



4-chloronicotinic acid (1.51g , 9.52mmol) and 4-methoxyaniline (1.17g, 9.52 mmol) were suspended in pyridine (0.75 g, 9.53mmol), *p*-TsOH (0.9g, 4.76 mmol) in 20 mL of water and 6mL acetone was added to the mixture. The reaction was raised to 75 ° C. The resulting system was refluxed overnight and then it was cooled to room temperature. The solid precipitated from the reaction mixture was purified by trituration in EtOAc (1.52g, yield%: 65).

^{1}H NMR (400 MHz, D_2O)：δppm 8.32 (s, 1H), 7.42 (s, 1H), 6.61 (d, J = 8.7 Hz, 2H), 6.41 (d, J = 8.4 Hz, 2H), 6.19 (d, J = 6.5 Hz, 1H), 3.36 (s, 3H)；^{13}C NMR (151 MHz, D_2O)：δppm 173.98, 155.66, 153.08, 152.12, 150.95, 150.31, 149.13, 131.63, 125.54, 124.28, 114.98, 113.92, 106.98, 106.00, 55.77, 54.95; IR (KBr, cm^{-1}): 3106.33 (m), 2493.21 (m), 1653.25 (s), 1508.58 (s), 1293.63 (s), 1246.98 (s), 1217.37 (s), 1171.59 (s), 1022.64 (s), 888.01 (s), 809.91 (s), 749.78 (s), 710.24 (s), 678.44 (s), 649.03 (s), 618.11 (s); MS (ESI): 245.80 (M+1); mp：275 ºC.

2. Crystal Structure Determination

The crystal structures of 4-ANAs were determined by single-crystal X-ray diffraction.

Data collection was carried out at 90 K on a Nonius kappaCCD diffractometer with MoKα radiation (λ = 0.71073 Å). Cell refinement and data reduction were done using SCALEPACK and DENZO-SMN. Structure solution and refinement were carried out using the SHELXS and SHELXL2016 programs, respectively.