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Synthesis of Some Aminopicolinic Acids

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Abstract: Some aminopicolinic acid derivatives have been synthesized and fully characterized. These pyridine derivatives were 4-aminopicolinic acid, 4-(4-aminophenylethynyl) picolinic acid and 4-(3-aminophenylethynyl) picolinic acid. In addition to these compounds, other substituted picolinic acids were made throughout the synthetic paths.

Key words: Aminopicolinic acid, Sinogoshira coupling reaction, synthetic paths.

1. Introduction

A number of aminopicolinic acid derivatives were synthesized. These pyridine derivatives include 4-aminopicolinic acid **3**, 4-(4-Aminophenylethynyl) picolinic acid **10** and 4-(3-Aminophenylethynyl) picolinic acid **11**. Such derivatives could be candidates to be used as ligands with transition metals [1]. For instance, 4-Amino-picolinic acid has been synthesized and used as a ligand [2]. However, there is a limited explanation of the synthetic procedure and also no sufficient amount of analytical data for this compound. It has also been reported that copper complexes of nicotinic acid with related pyridine derivatives possess superoxide dismutase (SOD) and antimicrobial activities [3]. Here, a short and economic procedure for the synthesis of 4-aminopicolinic acid is reported. Details regarding the syntheses of two additional extended aminopicolinic acids are also included in this contribution.

2. Experiment

2.1 Materials

Picolinic acid N-oxide, picolinic acid,

4-ethynylaniline, 3-ethynylaniline and bis-(triphenylphosphine) palladium(II) chloride were purchased from Sigma-Aldrich and used without any further purification.

2.2 Instrumentation

Melting points were measured on a Gallenkamp apparatus and are uncorrected. ¹H NMR and ¹³C NMR spectra were recorded on a Bruker AC-250 or a Bruker Avance 300 spectrometer or JEOL 600 MHz spectrometer. Residual proton signals from the deuteriated solvents were used as references [chloroform (¹H, 7.25 ppm; ¹³C, 77 ppm) and DMSO (¹H, 2.50 ppm; ¹³C, 39.7 ppm)]. Coupling constants were measured in Hz. All infrared spectra were recorded on Perkin-Elmer Spectrum RX/FT-IR system. Mass spectra were recorded on a Micromass Autospec M spectrometer.

2.3 Preparation of 4-Nitropicolinic Acid N-Oxide **2**

Picolinic acid N-oxide (10 gm, 71.94 mmol) was dissolved in a pre-cooled mixture of concentrated sulfuric acid (63 cm³) and fuming nitric acid (18 cm³) maintaining the temperature below 10 °C. The resulting clear mixture was heated at 120-130 °C for 2.5 h, cooled to room temperature and poured into a beaker containing water (367 cm³). The diluted mixture was

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stored in freezer overnight and the resulting yellow precipitate was collected by filtration and dried in vacuo to give the title compound as a pale yellow solid (7.03 gm, 38.21 mmol, 53% yield) [4-5]. No further purification was required, mp: 147-150 °C (148 °C in Ref. [4]). IR ν_{\max} (NaCl) (cm^{-1}): 3454 (br), 3253 (m), 3069 (w), 3005 (w), 2244 (s), 2124 (s), 1709 (s), 1615 (m), 1537 (m), 1441 (m); ^1H NMR [(CD_3) $_2\text{SO}$, 300 MHz, ppm]: δ 8.82 (1H, d, $J = 7.08$ Hz, ArCH), 8.66 (1H, s, ArCH), 8.49 (1H, m, ArCH); ^{13}C NMR [(CD_3) $_2\text{SO}$, 75 MHz, ppm]: δ 159.6 (CO), 144.7 (Ar-C), 141.4 (Ar-C), 138.9 (Ar-CH), 122.9 (Ar-CH), 121.7 (Ar-CH). NMR data was in accordance with the literature.

2.4 The Preparation of 4-Aminopicolinic Acid 3

A literature procedure [6] was adapted using catalytic hydrogenation in AcOH/Ac $_2$ O. 4-Nitropicolinic Acid *N*-Oxide (6.80 gm, 36.96 mmol) was dissolved in warm glacial acetic acid (300 cm 3) acetic anhydride (13 cm 3) with warming. The resulting mixture was stirred for 48 h at room temperature under hydrogen (60 psi) and in the presence of Pd/C (2.92 gm). The mixture was filtered through celite and the solvent was removed under reduced pressure to afford 4-aminopicolinic acid, which was recrystallised from hot H $_2$ O/EtOH (1:6 v/v) to give a white solid (2.42 gm, 17.54 mmol, 47%); mp: 266-268 °C (from H $_2$ O/EtOH) [263-265 °C (dec) from H $_2$ O in Ref. [2]]; IR ν_{\max} (KBr) (cm^{-1}): 3340-3275 (br), 3196-3081 (br), 1634 (s), 1391 (s).

Due to solubility difficulties in most deuterated solvents, a sample of 4-amino-2-picolinic acid was converted to the corresponding potassium salt using 1 equivalent of aqueous KOH. This allowed obtaining better NMR spectra. ^1H NMR [D $_2$ O, 300 MHz, ppm]: δ 7.82 (1H, s, ArCH), 6.95 (1H, s, ArCH), 6.41 (1H, s, ArCH); ^{13}C NMR [D $_2$ O/3 drops of (CD_3) $_2\text{SO}$, 75 MHz, ppm]: δ 173.09 (COOK), 156.59 (Ar-C), 154.59 (Ar-C), 148.85 (Ar-CH), 111.63 (Ar-CH), 110.63 (Ar-CH); MS m/z EI $^+$ (of the free acid C $_6$ H $_6$ N $_2$ O $_2$;

138.12): 138 (35), 94 (100), 84 (45), 67 (75). NMR data was in accordance with the literature.

2.5 The Preparation of Methyl 4-Chloro Picolinate Hydrochloride 5

A 250 cm 3 three-necked round-bottomed flask was equipped with stirring bar, gas bubbler and condenser in a distillation position. This flask was charged with SOCl $_2$ (60 cm 3 , 822.56 mmol) and heated at 40-45 °C then DMF (2 cm 3 , 25.86 mmol) was added drop wise by syringe. Picolinic acid (20.0 gm, 162.60 mmol) was then added to the solution in small portions (over 5 min) and the mixture was stirred at 40-45 °C for 15 min (evolution of SO $_2$ was observed). The temperature was raised slowly to 72 °C and the reaction mixture was stirred at the same temperature for 21 h. A relatively strong evolution of gases was observed at the beginning of the reaction. Excess SOCl $_2$ was removed by distillation at raised temperature in the presence of toluene (50 cm 3). The resulting acid chloride solution was allowed to stand at 40 °C (crystallization occurs at lower temperature). This acid chloride solution was transferred into another two-necked round-bottomed flask equipped with stirring bar, gas bubbler and containing a mixture of toluene (14 cm 3) and methanol (20 cm 3) and heated to 35-40 °C. The resulting suspension was stirred at room temperature for 1 h, filtered, and washed with toluene (2 \times 10 cm 3) and cold acetone (3 \times 15 cm 3). The product was transferred into a one necked round-bottomed and stirred in the acetone (60 cm 3) at 52 °C for 1 h, cooled to room temperature and stirred for 1 h, cooled to 5 °C and stirred for another 1 h, filtered and washed with cold acetone (3 \times 20 cm 3), and air-dried to give the desired compound as a white solid (16.24 gm, 84.58 mmol, 52% yield) [7]. No further purification was required; mp: 148-150 °C (146.5-147 °C in Ref. [7]); IR ν_{\max} (KBr) (cm^{-1}): 3317 (br), 3015 (w), 2593 (vbr), 1743 (s), 1616 (s), 1441 (s), 1301 (s); ^1H NMR [(CD_3) $_2\text{SO}$, 300 MHz, ppm]: δ 9.77 (1H, s, HCl), 8.67 (1H, ap d, $J = 3.40$ Hz, Ar-CH),

8.03 (1H, s, Ar-CH), 7.80 (1H, ap d, $J = 3.40$ Hz, Ar-CH), 3.86 (3H, s, OCH₃); ¹³C NMR [(CD₃)₂SO, 75 MHz, ppm]: δ 164.45 (C=O), 151.46 (Ar-C), 149.21 (Ar-C), 145.21 (Ar-CH), 127.97 (Ar-CH), 125.48 (Ar-CH), 53.53 (CH₃); MS m/z EI⁺ (C₇H₇Cl₂NO₂; 208.04): 208 (5), 171 (5), 1401 (25), 113 (100), 76 (75). NMR data was in accordance with the literature.

2.6 The Preparation of 4-Iodopicolinic Acid **6**

A 250 cm³ round-bottomed flask equipped with stirring bar, condenser in a distillation position and gas bubbler was charged with 4-chloromethylpicolinate hydrochloride (3.9 gm, 20.31 mmol), HI 57 % (20 cm³) and H₃PO₂ 50% (1 cm³). The reaction mixture was heated to 85 °C, where iodomethane (~2 cm³) started distilling off. The reaction mixture was stirred at 107 °C for 6 h and then cooled to room temperature. A yellow solid was formed and the resulting suspension was stirred at room temperature for 1 h, filtered, washed with cold water (3 × 20 cm³) and air-dried to give the desired compound as a yellow solid (4.09 gm, 18.43 mmol, 91% yield) [7]. No further purification was needed; mp: 192-193 °C (190-190.5 °C in Ref. [7]); IR ν_{\max} (KBr) (cm⁻¹): 3500-3380 (br), 1750 (m), 1601 (s), 1436 (m); ¹H NMR [(CD₃)₂SO, 300 MHz, ppm]: δ 8.41 (2H, s, 2 × Ar-CH), 8.17 (1H, s, Ar-CH), 6.48 (1H, br s, OH); ¹³C NMR [(CD₃)₂SO, 75 MHz, ppm]: δ 164.13 (C=O), 148.64 (Ar-C), 147.64 (Ar-C), 136.15 (Ar-CH), 133.65 (Ar-CH), 110.17 (Ar-CH); MS m/z EI⁺ (C₆H₄INO₂; 249.01): 249 (12), 206 (10), 205 (100), 128 (10), 78 (82). NMR data was in accordance with the literature.

2.7 The Preparation of Methyl 4-iodopicolinate **7**

A literature procedure [8] for esterification using catalytic amount of concentrated H₂SO₄ in MeOH was adapted. 4-iodopicolinic acid (5.02 gm, 20.16 mmol) was suspended in freshly distilled MeOH (110 cm³) and concentrated H₂SO₄ (4 cm³). The resulting mixture was refluxed for 24 h and the solvent was evaporated. The residual was dissolved in DCM (30

cm³), washed with H₂O (2 × 10 cm³), dried over Na₂SO₄ and filtered and the solvent was evaporated in vacuo to give a brown solid (2.05 gm, 7.80 mmol, 39% yield). The ¹H NMR and ¹³C NMR showed that the crude product was sufficiently clean, therefore no further purification was needed; mp: 70-71 °C; IR ν_{\max} (KBr) (cm⁻¹): 1725 (s), 1566 (s), 1557 (m), 1436 (s), 1381 (s), 1284 (s); ¹H NMR [(CD₃)₂SO, 300 MHz, ppm]: δ 8.40-8.33 (2H, m, Ar-CH), 8.08 (1H, s, Ar-CH), 3.88 (3H, s, CH₃); ¹³C NMR [(CD₃)₂SO, 150 MHz, ppm]: δ 164.0 (COOMe), 150.1 (Ar-C), 147.7 (Ar-C), 136.3 (Ar-CH), 133.4 (Ar-CH), 107.2 (Ar-CH), 52.7 (CH₃); MS m/z (EI⁺) 262.950 (2%, C₇H₆INO₂ requires 262.944): 263 (2), 234 (1), 233(5), 206 (2), 205(12), 144 (2), 143 (10), 141 (45), 140 (22), 113 (100), 112 (88).

2.8 The Preparation of 4-(4-Aminophenylethynyl) Picolinic Acid **10**

A literature procedure [9] for conducting Sinogoshira coupling reaction on similar systems was adapted.

Bis-(triphenylphosphine) palladium(II) chloride (0.07 gm, 0.10 mmol), CuI (40 gm, 2.09 mmol), 4-iodomethylpicolinate (1.0 gm, 3.80 mmol) and 4-ethynylaniline (0.53 gm, 4.53 mmol) were placed in a flame-dried schlenk tube. The tube was evacuated and flushed with argon for 5 min then 2 M NH₃ in EtOH (16.4 cm³) was added. The resulting mixture was stirred at room temperature for 48 h, diluted with DCM (15 cm³), filtered through a pad of celite and the filtrate was concentrated in vacuo. The residue was dissolved in DCM (20 cm³), washed with H₂O (15 cm³), dried over Na₂SO₄ and filtered and the solvent was removed in vacuo to give a brown solid (0.91 gm, 3.61 mmol). This solid (0.84 gm, 3.33 mmol) was refluxed for 2 h in HI ≥ 47% (35 cm³) and the resulting mixture was cooled to room temperature. A beige solid which was precipitated, filtered and stirred for 15 min in cold acetone (15 cm³) was filtered and dried to give a yellow solid which turns to dark red

solid of the 4-(4-aminophenylethynyl) picolinic acid (0.43 gm, 1.81 mmol, 54% yield). The ^1H NMR and ^{13}C NMR revealed that crude product was sufficiently pure, therefore no further purification was needed. mp 154-156 °C; IR ν_{max} (NaCl) (cm^{-1}): 3558-3215 (s and vbr), 2258 (m), 2131 (w), 1668 (s); ^1H NMR [(CD₃)₂SO, 600 MHz, ppm]: δ 8.75 (1H, ap d, $J = 5.3$ Hz, Ar-CH), 8.52 (1H, s, Ar-CH), 8.21 (1H, ap s, Ar-CH), 8.04 (1H, d, $J = 16.6$ Hz, Ar-CH), 7.76 (2H, ap d, $J = 8.0$ Hz, Ar-CH), 7.49 (1H, d, $J = 16.6$ Hz, Ar-CH), 7.13 (2H, ap d, $J = 8.0$ Hz, NH₂); ^{13}C NMR [(CD₃)₂SO, 150 MHz, ppm]: δ 161.9 (C=O), 153.7 (Ar-C), 153.6 (Ar-C), 143.7 (Ar-C), 142.0 (Ar-C), 139.9 (Ar-CH), 129.9 (4 \times Ar-CH), 124.5 (Ar-CH), 122.7 (Ar-CH), 121.6 (C), 119.6 (C); MS m/z (EI⁺) 239.483 (80%, C₁₄H₁₀N₂O₂ requires 238.074): 240 (80), 196 (100), 180 (32), 168 (64), 128 (68), 93 (58), 51 (34); MS for the potassium salt m/z (EI⁺) 277.067 (100%, C₁₄H₉KN₂O₂ requires 276.030) 278 (100), 202 (72), 183 (56), 152 (28), 77 (72), 51 (64).

2.9 The Preparation of 4-(3-Aminophenylethynyl) Picolinic Acid II

A procedure of Ref. [9] for conducting Sinogoshira coupling reaction on similar systems was adapted. Bis-(triphenylphosphine) palladium(II) chloride (0.07 gm, 0.10 mmol), CuI (0.40 gm, 2.09 mmol), 4-iodomethylpicolinate (1.0 gm, 3.80 mmol) and 3-ethynylaniline (0.53 gm, 4.53 mmol) were placed in a flame-dried schlenk tube. The tube was flushed with argon for 5 min then 2 M NH₃ in EtOH (16.4 cm³) was added. The resulting mixture was stirred at room temperature for 48 h, diluted with DCM (15 cm³), filtered through a pad of celite and the filtrate was concentrated in vacuo. The residue was dissolved in DCM (20 cm³), washed with H₂O (15 cm³) and filtered. The organic layer was separated, dried over Na₂SO₄ and filtered, and then the solvent was removed in vacuo to give a brown solid (0.83 gm, 3.29 mmol). This solid (0.10 gm, 0.40 mmol) was refluxed for 2 h in HI 47% (5 cm³) and the resulting

mixture was cooled to room temperature. A yellow solid was precipitated, filtered, stirred for 15 min in cold acetone, filtered and dried to give an orange solid (0.04 gm, 0.17 mmol, 43% yield) of the 4-(3-aminophenylethynyl) picolinic acid. The ^1H NMR and ^{13}C NMR revealed that crude product was sufficiently pure, therefore no further purification was needed. mp: 221-223 °C (dec); IR ν_{max} (NaCl) (cm^{-1}): 3594-3187 (vs and vbr), 2558 (m), 2132 (w), 1660 (s); ^1H NMR [(CD₃)₂SO, 600 MHz, ppm]: δ 8.77 (1H, d, $J = 5.0$ Hz, Ar-CH), 8.43 (1H, s, Ar-CH), 8.06 (1H, ap d, $J = 5.0$ Hz, Ar-CH), 7.90 (1H, d, $J = 14.9$ Hz, Ar-CH), 7.76 (1H, d, $J = 6.5$ Hz, Ar-CH), 7.57 (2H, s, NH₂), 7.53 (1H, t, $J = 18.3$ Hz, Ar-CH), 7.32 (1H, d, $J = 6.1$ Hz, Ar-CH); ^{13}C NMR [(CD₃)₂SO, 150 MHz, ppm]: δ 164.4 (C=O), 148.4 (Ar-C), 147.6 (Ar-C), 146.4 (Ar-C), 137.3 (Ar-C), 135.1 (Ar-CH), 134.1 (Ar-CH), 130.3 (Ar-CH), 126.1 (Ar-CH), 125.6 (Ar-CH), 124.2 (Ar-CH), 122.8 (Ar-CH), 122.4 (C), 121.0 (C); MS m/z (EI⁺) 239.632 (44%, C₁₄H₁₀N₂O₂ requires 238.074): 240.14 (44), 195 (100), 168 (20), 128 (12), 98 (6), 58 (6); MS for the potassium salt m/z (EI⁺) 276.217 (100%, C₁₄H₉KN₂O₂ requires 276.030): 277 (100), 201 (20), 183 (18), 152 (12), 77 (28), 51 (31).

2.10 The Preparation of Methyl 4-cyanopicolinate 12

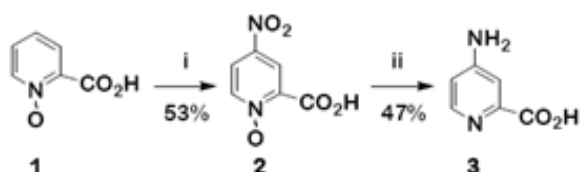
An adapted textbook procedure was followed [10]. A schlenk tube was flame-dried, flushed with argon. Copper(I) cyanide (0.17 gm, 1.90 mmol) and 4-iodomethylpicolinate (0.45 gm, 1.71 mmol) were placed in the schlenk tube, evacuated and flushed with argon. Dry DMF (5 cm³) was added *via* syringe and the reaction mixture was stirred at 110-130 °C for 4 h. The resulting mixture was diluted with DCM (10 cm³), filtered through a pad of celite and the solvent was removed in vacuo to give the desired compound as a beige solid (0.24 gm, 1.48 mmol, 87% yield), which did not require further purification; mp: 139-140 °C; IR ν_{max} (KBr) (cm^{-1}): 3100-3056 (m), 2242 (m), 1724 (s), 1450 (s), 1408 (s), 1299 (s); ^1H NMR [(CD₃)₂SO, 600 MHz, ppm]: δ 8.99 (1H, s, Ar-CH), 8.44 (1H, s,

Ar-CH), 8.16 (1H, s, Ar-CH), 3.93 (3H, s, OCH₃); ¹³C NMR [(CD₃)₂SO, 150 MHz, ppm]: δ 163.8 (COOMe), 151.0 (Ar-C), 148.4 (Ar-C), 129.1 (Ar-CH), 126.5 (Ar-CH), 120.9 (Ar-CH), 116.1 (CN), 52.9 (OCH₃); MS *m/z* (EI⁺) 161.815 (10%, C₈H₆N₂O₂ requires 162.043): 162 (10), 132 (82), 103 (100), 76 (84), 59 (52).

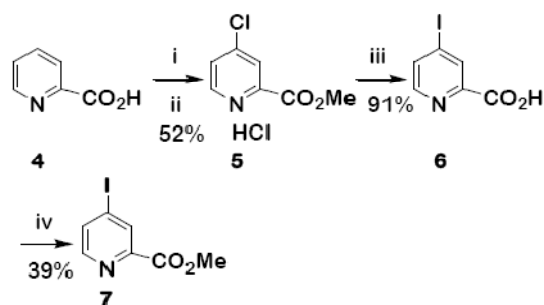
3. Results and Discussion

The 4-aminopicolinic acid **3** was synthesized by the nitration of picolinic acid *N*-oxide **1** using a mixture of sulfuric acid and fuming nitric acid. The resulting 4-nitropicolinic acid *N*-oxide **2** was reduced to the corresponding 4-aminopicolinic acid **3** using catalytic hydrogenation (Scheme 1). The synthesis of extended aminopicolinic acid derivatives **10** and **11** required the preparation of 4-iodomethylpicolinate **7**. The latter was prepared through a multi-step reaction starting from treatment of picolinic acid **4** with thionyl chloride in the presence of catalytic amount of DMF at 72 °C. Resulting mixture was treated with methanol/toluene at 40 °C to produce 4-chloromethylpicolinate hydrochloride **5**. This was treated with HI and H₃PO₂ at 107 °C for 6 h to produce 4-iodopicolinic acid **6** as a yellow solid. 4-iodopicolinic acid **6** was then converted to the corresponding methyl ester **7** by using catalytic amount of concentrated sulfuric acid in methanol at reflux (Scheme 2).

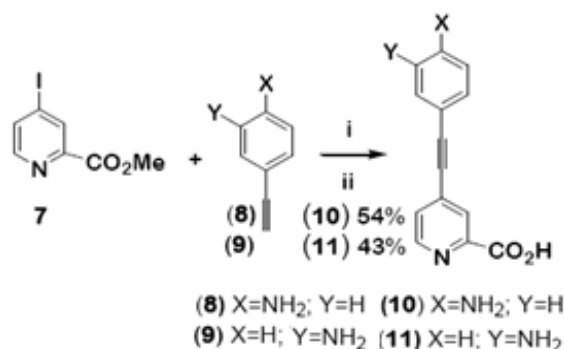
A Sinogoshira coupling reaction was used to couple 4-iodomethylpicolinate **7** to both 4-ethynylaniline **8** and 3-ethynylaniline **9** to yield 4-(4-aminophenylethynyl) picolinic acid **10** and 4-(3-aminophenylethynyl) picolinic acid **11**, respectively. The coupling reaction was carried out by



Scheme 1 The formation of 4-aminopicolinic acid. Reagents and conditions: (i) fuming HNO₃/H₂SO₄, 120 °C to 130 °C, 2.5 h; (ii) H₂, Pd/C, AcOH/Ac₂O, 48 hr, rt, 60 psi.



Scheme 2 The synthesis of the precursor methyl 4-iodopicolinate. Reagents and conditions: (i) SOCl₂, DMF, 40-72 °C, 21 h; (ii) MeOH/toluene, rt, 1 h; (iii) HI, H₃PO₂, 85-107 °C, 6 h; (iv) MeOH, cat. conc. H₂SO₄, reflux, 24 h.

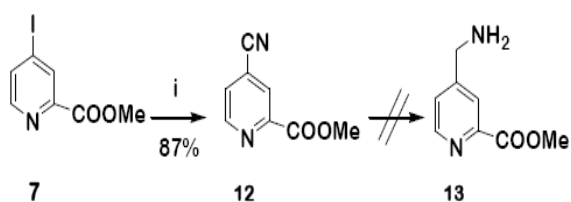


Scheme 3 The use of Sinogoshira coupling reaction to obtain the extended aminopicolinic acids. Reagents and conditions: (i) (Ph₃P)₂PdCl₂, CuI, 2 M NH₃ in EtOH, rt, 48 h; (ii) HI 47%, reflux, 2 h.

bis-(triphenylphosphine) palladium(II) chloride in the presence of copper(I) iodide and 2 M ammonia in ethanol. Subsequent acid hydrolysis using hydriodic acid at reflux gave the desired aminopicolinic acids **10** and **11** (Scheme 3). Efforts were made to synthesize 4-(aminomethyl) picolinic acid **13** by the reduction of 4-cyano-2-methylpicolinate **12**, which was easily prepared through a reaction between copper(I) cyanide and 4-iodomethylpicolinate **7** in dry DMF. The catalytic hydrogenation compound **12** using Pd/C in pyridine to reduce the cyano group was unsuccessful (Scheme 4). The pyridine was used as a solvent due to that compound **12** which was insoluble in most commonly used organic solvents.

4. Conclusions

In conclusion, the synthesis of a number of aminopicolinic acid derivatives has been achieved in a



Reagents and conditions: (i) CuCN, DMF, 110 to 130 °C, 4h

Scheme 4 Attempts to reducing the methyl 4-caynopicolinate.

concise and straightforward manner. The reduction of the nitrile group of compound **12** was the only major obstacle faced in the synthesis of 4-(aminomethyl) picolinic acid **13**.

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