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SYNTHESIS OF 5-AMINO OR 4-AMINO SUBSTITUTED 7-AZA-ISOINDOLIN-1-ONES

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Abstract – A simple and convenient route for the synthesis of a series of 5-amino or 4-amino substituted 7-aza-isoindolin-1-ones is described. Amino substituted pyridine derivatives were cyclized with different amines in alkaline condition to give the desired products.

INTRODUCTION

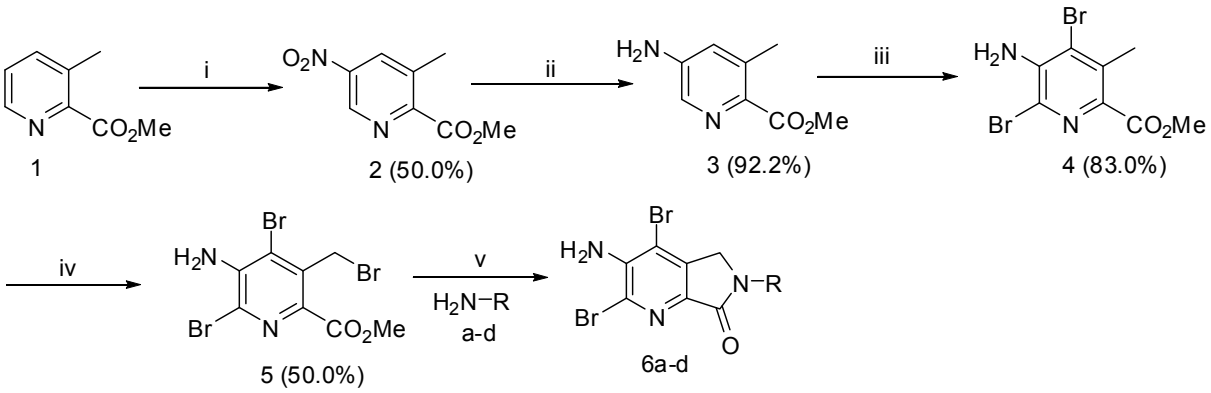
Isoindolin-1-one and its aza-heterocyclic derivatives are well known by synthetic and biological chemists. They are important structure units present in many bioactive molecules that possess a wide spectrum of biological activities and have been therefore the subject of continuing chemical study.[1-4] With further exploration, it is found that the substitution of amino group on the aromatic nuleus of some isoindolinones can increase the bioactivity or even lead to a new type of activity.[5-8] A few methods for the synthesis of amino substituted 4-aza,[9] 5-aza[10] and 6-aza[11,12] isoindolinones are reported. However, there are no data on the 5-amino or 4-amino substituted analogs of 7-aza-isoindolin-1-one in the literature.

At the onset of the research, we examined the synthesis of amino substituted 7-aza-isoindolin-1-one derivatives through the construction of 7-aza-isoindolinones followed by amino or nitro (which can be reducted to amino easily) substitution on the pyridine ring. However, there are no obvious product observed when using $NaNH_2$ or HNO_3/H_2SO_4 with 7-aza-isoindolinones. We decided to synthesize these compounds with another strategy: amino substituted pyridine compounds will be established before fusing of pyrrolidinones.

RESULTS AND DISCUSSION

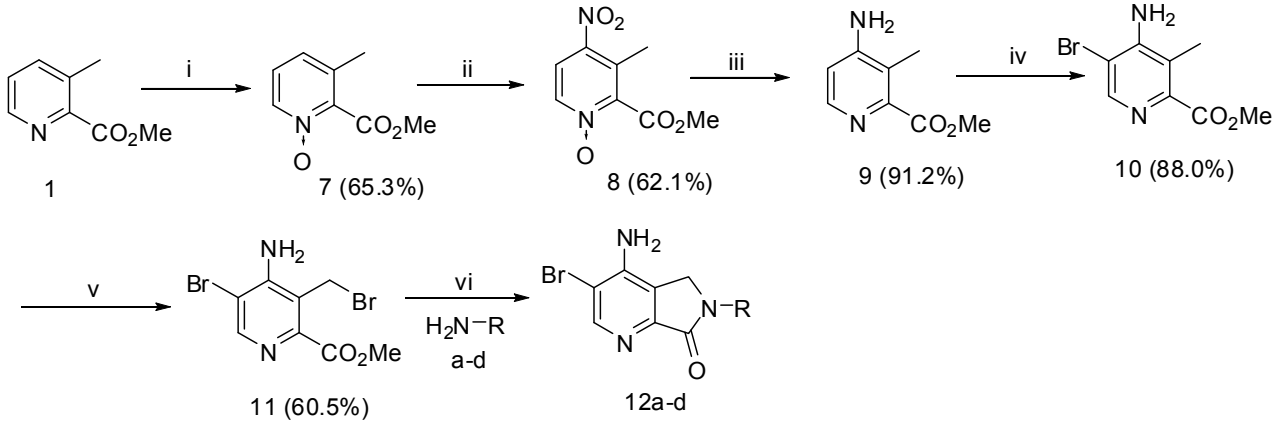
5-Amino substituted analogs of 7-aza-isoindolin-1-one were synthesized by the methodology as shown in **Scheme 1**. The nitration of **1** with tetrabutylammonium nitrate method afforded **2** under mild

conditions.[13,14] Compound **3** was obtained by Pd/C catalyzed hydrogenation reduction. Compound **4** was given by the electrophilic substitution on **3** in the NBS/NH_4OAc system.[15] The free radical reaction of *N*-bromosuccinimide (NBS) / azodiisobutyronitrile (AIBN) with **4** afforded **5** at reflux. Different amines **(a-d)** were reacted with **5** in alkaline condition to form the final 5-amino-4,6-dibromo-7-aza-iso-indolinones **6a-d**.[16,17]



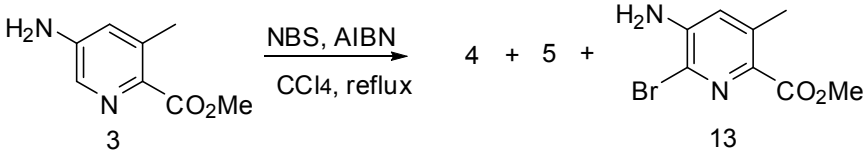
Scheme 1. Reagents and conditions: (i) $Bu_4N^+NO_3^-$, $(CF_3CO)_2O$, CH_2Cl_2, rt; (ii) 10% Pd/C, H_2, MeOH, rt; (iii) NBS, NH_4OAc, MeCN; (iv) NBS, AIBN, CCl_4, reflux; (v) K_2CO_3, MeCN, rt to reflux.

4-Amino substituted analogs of 7-aza-isoindolin-1-one were synthesized according to **Scheme 2**, with similar thinking way. The difference is that the oxidation of pyridine N atom is necessary for involving nitro group on the para-position.[18] Moreover, the amount of NBS used to synthesis **10** was 1.1 equivalents of **9**, while **4** was synthesized by 2.0 equivalents NBS with 1.0 equivalent **3**. This is due to the strong electron-donating effect of amino group which can improve the nucleophilic capability of its ortho-position.



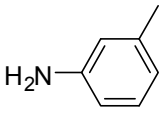
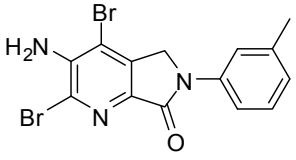
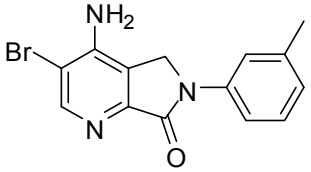
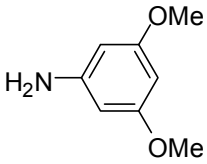
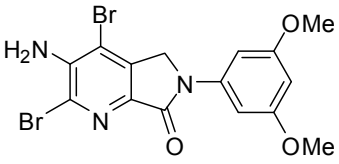
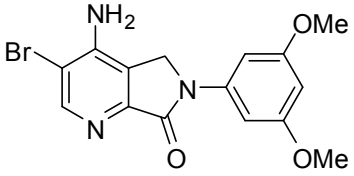
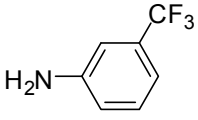
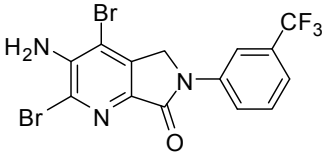
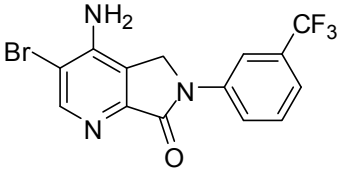
Scheme 2. Reagents and conditions: (i) 30% H_2O_2, HOAc, rt to 80 °C; (ii) fuming HNO_3, H_2SO_4, 95-100 °C; (iii) 10% Pd/C, H_2, MeOH, rt; (iv) NBS, NH_4OAc, MeCN; (v) NBS, AIBN, CCl_4, reflux; (vi) K_2CO_3, MeCN, rt to reflux.

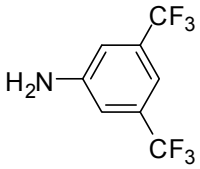
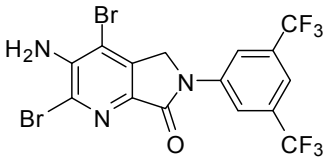
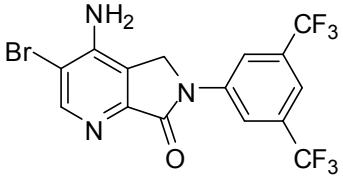
Methyl bromination of **2** or **8** was hard to proceed, because the polarization of nitro group weakened the conjugated system which can stabilize the generated free radical. In addition, though reaction (**iii)** and **(iv)** in **Scheme 1** are both bromination reaction, the mechanism between them is different. Reaction (**iii**) is electrophilic substitution on pyridine ring. But (**iv**) is free radical reaction on methyl group. A strange phenomenon was that, if **3** was reacted with NBS/AIBN at reflux in CCl_4 directly (free radical conditions), the mixture would generated including **4**, **5**, **13** and other by-products, which were hard to be separated. It may be attributed to the strong electron-donating effect of amino group. Similar results occurred on **9**.



It was noticed that the yields of **6a-d** and **12a-d** were relevant to the amines used (**Table1**). The products of amines **a** and **b** were relatively of high yield. It may be due to the nucleophilicity of amino group elevated by the electron-donating group on the benzene. The products of amine **c** were lower than **d**. It might be that the exsitence of two trifluoromethyl group leads to generate nitrogen anion in alkaline condition, which is beneficial for the nucleophilic attack to bromomethyl group. This assumption needs to be proved by further studies.

Table 1. Amines (**a-d**) and corresponding amino substituted 7-aza-isoindolinones (**6a-d** and **12a-d**)

Entry	Amines	**6a-d**	Yield(%)	**12a-d**	Yield(%)
a			65.6%		66.7%
b			70.3%		60.1%
c			30.2%		43.5%

d			59.8%		55.3%

EXPERIMENTAL

Melting points were determined on a SGW X-4 melting point instrument and were uncorrected. ^{1}HNMR and ^{13}CNMR spectra were carried out using Bruker Advance Ⅲ 400 MHz spectrometer and MERCURYplus 300 spectrometer. HRMS was measured on a Waters ACQUITY^{TM} UPLC & Q-TOF MS Premier system. Column chromatography was performed using Silica Gel (200-300 mesh) with the eluents indicated.

General protocol for the synthesis of compounds 6a-d and 12a-d

Amines **a-d** (1.1 equiv) and K_2CO_3 (1.5 equiv) were added to a solution of methyl 5-amino-4,6-dibromo-3-(bromomethyl)picolinate **5** or methyl 4-amino-5-bromo-3-(bromomethyl)picolinate **11** (1.0 equiv) in MeCN under the protection of nitrogen. The resulting mixture was stirred at room temperature for 2 h and then heated to reflux for another 5 h. The reaction mixture was cooled to room temperature, filtered and concentrated in vacuo. The crude residue was purified by column chromatography (conditions specified). And the resulting product was obtained by concentrating appropriate fractions. The yields were specified for each individual case.

5-Amino-4,6-dibromo-2-(*m*-tolyl)-7-aza-isoindolin-1-one (6a)

6a was afforded by column chromatography (100:1 CH_2Cl_2/MeOH) as a white solid (yield 65.6%, mp >300 °C). ^{1}HNMR (300MHz, DMSO-d_6) δ: 7.67~7.72 (m, 2H, NCC<u>H</u>), 7.29 (t, 1H, J = 7.5 Hz, CH_3CCHC<u>H</u>), 6.98 (d, 1H, J = 6.6 Hz, CH_3CC<u>H</u>CH), 6.43 (s, 2H, NH_2), 4.81 (s, 2H, C<u>H</u>$_2$N), 2.33 (s, 3H, C<u>H</u>$_3$). ^{13}CNMR (400MHz, DMSO-d_6) δ: 163.4, 143.1, 139.2, 138.2, 138.1, 137.5, 128.7, 128.6, 124.9, 119.5, 116.3, 109.2, 48.3, 21.2. ESI-HRMS: calcd for $C_{14}H_{12}N_3OBr_2(MH^+)$, 395.9347, found 395.9330.

5-Amino-4,6-dibromo-2-(3,5-dimethoxyphenyl)-7-aza-isoindolin-1-one (6b)

6b was afforded by column chromatography (100:1 CH_2Cl_2/MeOH) as a grey solid (yield 70.3%, mp >300 °C). ^{1}HNMR (400MHz, DMSO-d_6) δ: 7.11 (d, 2H, J = 2.0 Hz, NCC<u>H</u>), 6.42 (s, 2H, NH_2), 6.35 (t, 1H, J = 2.0 Hz, CC<u>H</u>C), 4.82 (s, 2H, C<u>H</u>$_2$N), 3.78 (s, 6H, C<u>H</u>$_3$O). ^{13}CNMR (400MHz, DMSO-d_6) δ: 163.5, 160.6, 143.1, 140.8, 138.0, 137.3, 128.7, 109.1, 97.6, 96.0, 55.3, 48.4. ESI-HRMS: calcd for $C_{15}H_{14}N_3O_3Br_2$ (MH^+), 441.9402, found 441.9395.

5-Amino-4,6-dibromo-2-[3-(trifluoromethyl)phenyl]-7-aza-isoindolin-1-one (6c)

6c was afforded by column chromatography (200:1 CH_2Cl_2/MeOH) as a white solid (yield 30.2%, mp

293~295 °C). ^{1}HNMR (400MHz, DMSO-d_6) δ: 8.39 (s, 1H, NCCHC), 8.13 (dd, 1H, J = 8.0 Hz, 2.0 Hz, NCCHCH), 7.68 (t, 1H, J = 8.0 Hz, NCCHCH), 7.54 (d, 1H, J = 8.0 Hz, CF_3CCHCH), 6.50 (s, 2H, NH_2), 4.95 (s, 2H, CH_2N). ^{13}CNMR (400MHz, DMSO-d_6) δ: 163.8, 143.4, 140.0, 138.4, 136.8, 130.1, 129.1~130.1, 128.8, 122.7~125.4, 122.4, 120.4, 115.1~115.2, 108.9, 48.3. ESI-HRMS: calcd for $C_{14}H_9N_3OF_3Br_2$ (MH^+), 449.9064, found 449.9078.

5-Amino-4,6-dibromo-2-[3,5-bis(trifluoromethyl)phenyl]-7-aza-isoindolin-1-one (6d)

6d was afforded by column chromatography (200:1 CH_2Cl_2/MeOH) as a white solid (yield 59.8%, mp >300 °C). ^{1}HNMR (400MHz, DMSO-d_6) δ: 8.60 (s, 2H, NCCH), 7.87 (s, 1H, CCHC), 6.57 (s, 2H, NH_2), 5.04 (s, 2H, CH_2N). ^{13}CNMR (400MHz, DMSO-d_6) δ: 164.2, 143.7, 141.1, 138.6, 136.2, 130.7~131.1, 128.9, 121.8~124.5, 118.6, 116.7, 108.7, 48.5. ESI-HRMS: calcd for $C_{15}H_8N_3OF_6Br_2$ (MH^+), 517.8938, found 517.8929.

4-Amino-5-bromo-2-(*m*-tolyl)-7-aza-isoindolin-1-one (12a)

12a was afforded by column chromatography (100:1 CH_2Cl_2/MeOH) as a white solid (yield 66.7%, mp 274~276 °C). ^{1}HNMR (300MHz, DMSO-d_6) δ: 8.39 (s, 1H, NCH), 7.64~7.69 (m, 2H, NCCH), 7.32 (t, 1H, J = 7.8 Hz, NCCHCH), 7.01 (d, 1H, J = 7.8 Hz, CH_3CCHCH), 6.85 (s, 2H, NH_2), 4.76 (s, 2H, NCH_2), 2.34 (s, 3H, CH_3). ^{13}CNMR (400MHz, DMSO-d_6) δ: 164.9, 151.6, 148.5, 147.0, 139.4, 138.3, 128.9, 125.0, 121.1, 119.5, 116.2, 106.6, 46.9, 21.3. ESI-HRMS: calcd for $C_{14}H_{13}N_3OBr$ (MH^+), 318.0242, found 318.0239.

4-Amino-5-bromo-2-(3,5-dimethoxyphenyl)-7-aza-isoindolin-1-one (12b)

12b was afforded by column chromatography (100:1 CH_2Cl_2/MeOH) as a white solid (yield 60.1%, mp 284~287 °C). ^{1}HNMR (300MHz, DMSO-d_6) δ: 8.56 (s, 1H, NCH), 7.53 (s, 2H, NH_2), 7.08 (s, 2H, NCCH), 6.41 (s, 1H, CCHC), 3.71 (s, 6H, CH_3O). ^{13}CNMR (400MHz, DMSO-d_6) δ: 162.7, 160.7, 149.5, 147.5, 144.6, 140.3, 121.1, 105.8, 97.6, 96.4, 55.3, 47.8. ESI-HRMS: calcd for $C_{15}H_{15}N_3O_3Br$ (MH^+), 364.0297, found 364.0281.

4-Amino-5-bromo-2-[3-(trifluoromethyl)phenyl]-7-aza-isoindolin-1-one (12c)

12c was afforded by column chromatography (150:1 CH_2Cl_2/MeOH) as a white solid (yield 43.5%, mp >300 °C). ^{1}HNMR (400MHz, DMSO-d_6) δ: 8.44 (s, 1H, NCH), 8.24 (s, 1H, NCCHC), 8.14 (d, 1H, J = 8.0 Hz, NCCHCH), 7.72 (t, 1H, J = 8.4 Hz, NCCHCH), 7.55 (d, 1H, J = 8.0 Hz, NCCHCHCH), 6.84 (s, 2H, NH_2), 4.87 (s, 2H, NCH_2). ^{13}CNMR (400MHz, DMSO-d_6) δ: 165.6, 152.0, 148.2, 147.0, 140.1, 130.3, 129.3~130.1, 122.7~125.4, 122.2, 121.3, 120.4, 114.8, 106.8, 46.8. ESI-HRMS: calcd for $C_{14}H_{10}N_3OF_3Br$ (MH^+),371.9959, found 371.9952.

4-Amino-5-bromo-2-[3,5-bis(trifluoromethyl)phenyl]-7-aza-isoindolin-1-one (12d)

12d was afforded by column chromatography (150:1 CH_2Cl_2/MeOH) as a white solid (yield 55.3%, mp

>300 °C). ^{1}HNMR (400MHz, DMSO-d_6) δ: 8.54 (s, 1H, NC<u>H</u>), 8.50 (s, 2H, NCC<u>H</u>), 7.98 (s, 1H, CC<u>H</u>C), 7.32 (s, 2H, NH_2), 5.00 (s, 2H, NC<u>H_2</u>). ^{13}CNMR (400MHz, DMSO-d_6) δ: 164.0, 149.1, 148.8, 144.6, 140.6, 130.5~131.5, 121.7~124.4, 121.5, 118.6, 117.4, 106.3, 47.5. ESI-HRMS: calcd for $C_{15}H_9N_3OF_6Br$ (MH^+), 439.9833, found 439.9807.

Methyl 3-methyl-5-nitropicolinate (2)

Trifluoroacetic anhydride (3.06 mL, 0.022 mol) was added dropwise at 0 °C to a solution of methyl 3-methylpicolinate **1** (1.52 g, 0.010 mol) and tetrabutylammonium nitrate (3.35 g, 0.011 mol) in CH_2Cl_2 (50 mL). The mixture was stirred at room temperature for 18 h after which it was neutralized with saturated aqueous Na_2CO_3 solution, extracted with CH_2Cl_2 and the organic layer was dried (anhydrous Na_2SO_4), concentrated, and purified by chromatography (6:1 cyclohexane/EtOAc) to afford **2** as white solid (0.98 g, yield 50.0%, mp 80~82 °C). ^{1}HNMR (300MHz, $CDCl_3$): δ 9.30 (s, 1H, NC<u>H</u>), 8.41 (s, 1H, NCHCC<u>H</u>, 4.02 (s, 3H, C<u>H_3</u>O), 2.70 (s, 3H, C<u>H_3</u>).

Methyl 5-amino-3-methylpicolinate (3)

10% Pd/C (50 mg) was added to a solution of methyl 3-methyl-5-nitropicolinate **2** (0.96 g, 4.9 mmol) in MeOH (15 mL) at room temperature. The resulting mixture was stirred under H_2 (1 atm) for 2 h and then filtered. The filtrate was concentrated in vacuo and the residue was purified by chromatography (50:1 CH_2Cl_2/MeOH) to afford **3** as offwhite solid (0.75 g, yield 92.2%, mp 145~146 °C). ^{1}HNMR (300MHz, $CDCl_3$): δ 8.00 (d, 1H, J = 2.4 Hz, NC<u>H</u>), 6.79 (d, 1H, J = 2.4 Hz, NCHCC<u>H</u>), 3.92 (s, 3H, C<u>H_3</u>O), 2.56 (s, 3H, C<u>H_3</u>).

Methyl 5-amino-4,6-dibromo-3-methylpicolinate (4)

N-Bromosuccinimide (2.14 g, 12 mmol) was added to a solution of methyl 5-amino-3-methylpicolinate **3** (0.98 g, 6 mmol) and NH_4OAc (31 mg, 0.4 mmol) in MeCN (20 mL). The mixture was stirred at room temperature for 5 h and then concentrated in vacuo. The residue was purified by chromatography (6:1 cyclohexane/EtOAc) to afford **4** as faint yellow solid (1.07 g, yield 83.0%, mp 146~148 °C). ^{1}HNMR (300MHz, $CDCl_3$) δ: 5.01 (s, 2H, N<u>H_2</u>), 3.93 (s, 3H, OC<u>H_3</u>), 2.67 (s, 3H, C<u>H_3</u>).

Methyl 5-amino-4,6-dibromo-3-(bromomethyl)picolinate (5)

A mixture of methyl 5-amino-4,6-dibromo-3-methylpicolinate **4** (400 mg, 1.24 mmol) in CCl_4 (20 mL) with *N*-bromosuccinimide (264 mg, 14.8 mmol) and azodiisobutyronitrile (90 mg, 0.54 mmol) was refluxed for 5 h. The reaction mixture was then cooled to room temperature, filtered and concentrated under reduced pressure. The residue was purified by chromatography (10:1 cyclohexane/acetone) to afford **5** as yellow solid (250 mg, yield 50.0%, mp 84~86 °C). ^{1}HNMR (300MHz, $CDCl_3$) δ: 5.14 (s, 2H, N<u>H_2</u>), 5.11 (s, 2H, BrC<u>H_2</u>), 3.97 (s, 3H, C<u>H_3</u>O)

2-(Methyoxycarbonyl)-3-methylpyridine 1-oxide (7)

Cold (5 °C) 30% hydrogen peroxide (7 mL, 66 mmol) was added to a solution of methyl 3-methylpicolinate **1** (5 g, 33 mmol) in glacial AcOH (15 mL) at room temperature. The mixture was heated in an oil bath for 24 h, with the internal temperature adjusted to 80±5 °C. The excess AcOH and water are removed under reduced pressure. The residue was cooled to 0-5 °C and neutralized with saturated Na_2CO_3 solution, extracted with CH_2Cl_2 and the organic layer was dried (anhydrous Na_2SO_4), concentrated, and purified by chromatography (50:1 CH_2Cl_2/MeOH) to give **7** as paint yellow liquid (3.6 g, yield 65.3%). ^{1}HNMR (300MHz, $CDCl_3$): δ 8.05 (d, 1H, *J* = 3.2 Hz, NC<u>H</u>), 7.20 (d, 1H, *J* = 3.3 Hz, NCHCHC<u>H</u>), 7.10~7.16 (m, 1H, NCHC<u>H</u>), 3.99 (s, 3H, C<u>H</u>$_3$O), 2.26 (s, 3H, C<u>H</u>$_3$).

2-(Methyoxycarbonyl)-3-methyl-4-nitropyridine 1-oxide (8)

2-(Methyoxycarbonyl)-3-methylpyridine 1-oxide **7** (2.3 g, 13.8 mmol) was added to cold conc.sulfuric acid (15 mL). And fuming yellow nitric acid (4 mL) was added dropwise to the solution for 20 min. Then the mixture was heated slowly to 95-100 °C and reacted for 5 h. When the temperature was cooled down, the mixture was neutralized with saturated aqueous Na_2CO_3 solution at 0 °C, extracted with CH_2Cl_2 and the organic layer was dried (anhydrous Na_2SO_4), concentrated, and purified by chromatography (75:1 CH_2Cl_2 /MeOH) to afford **8** as faint yellow solid (1.8 g, yield 62.1%, mp 166~168 °C). ^{1}HNMR (300MHz, $CDCl_3$): δ 8.15 (d, 1H, *J* = 3.3 Hz, NC<u>H</u>), 8.02 (d, 1H, *J* = 3.4 Hz, NCHC<u>H</u>), 4.06 (s, 3H, C<u>H</u>$_3$O), 2.55 (s, 3H, C<u>H</u>$_3$).

Methyl 4-amino-3-methylpicolinate (9)

10% Pd/C (50 mg) was added to a solution of 2-(methyoxycarbonyl)-3-methyl-4- nitropyridine 1-oxide **8** (0.7 g, 3.3 mmol) in MeOH (15 mL) at room temperature. The resulting mixture was stirred under H_2 (1 atm) for 4 h and then filtered. The filtrate was concentrated in vacuo and the residue was purified by chromatography (50:1 CH_2Cl_2/MeOH) to afford **9** as white solid (0.5 g, yield 91.2%, mp 65~67 °C). ^{1}HNMR (300MHz, $CDCl_3$): δ 8.18 (d, 1H, *J* = 2.8 Hz, NC<u>H</u>), 6.65 (d, 1H, *J* = 2.7 Hz, NCHC<u>H</u>), 4.28 (s, 2H, N<u>H</u>$_2$), 3.97 (s, 3H, C<u>H</u>$_3$O), 2.55 (s, 3H, C<u>H</u>$_3$).

Methyl 4-amino-5-bromo-3-methylpicolinate (10)

N-Bromosuccinimide (1.22 g, 6.8 mmol) was added to a solution of methyl 4-amino-3-methylpicolinate **9** (1.03 g, 6.2 mmol) and NH_4OAc (53 mg, 0.7 mmol) in MeCN (20 mL). The mixture was stirred at room temperature for 1 h and then concentrated in vacuo. The residue was purified by chromatography (100:1 CH_2Cl_2/MeOH) to afford **10** as faint yellow solid (1.33 g, yield 88.0%, mp 135~137 °C). ^{1}HNMR (300MHz, $CDCl_3$) δ: 8.47(s, 1H, NC<u>H</u>), 4.89 (s, 2H, N<u>H</u>$_2$), 4.01 (s, 3H, OC<u>H</u>$_3$), 2.50 (s, 3H, C<u>H</u>$_3$).

Methyl 4-amino-5-bromo-3-(bromomethyl)picolinate (11)

A mixture of methyl 4-amino-5-bromo-3-methylpicolinate **10** (500 mg, 2.0 mmol) in CCl_4 (25 mL) with *N*-bromosuccinimide (427 mg, 2.4 mmol) and azodiisobutyronitrile (164 mg, 1.0 mmol) was refluxed for

1 h. The reaction mixture was then cooled to room temperature, filtered and concentrated under reduced pressure. The residue was purified by chromatography (200:1 CH_2Cl_2/MeOH) to afford **11** as yellow solid (392 mg, 60.5%, mp 228~231 °C). ^{1}HNMR (300MHz, $CDCl_3$) δ: 8.34 (s, 1H, NC<u>H</u>), 5.10 (s, 2H, N<u>H</u>$_2$), 4.77 (s, 2H, BrC<u>H</u>$_2$), 3.88 (s, 3H, C<u>H</u>$_3$O).

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