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SYNTHESIS OF 4-METHOXY AND 5-METHOXY SUBSTITUTED 7-AZA-ISOINDOLIN-1-ONES

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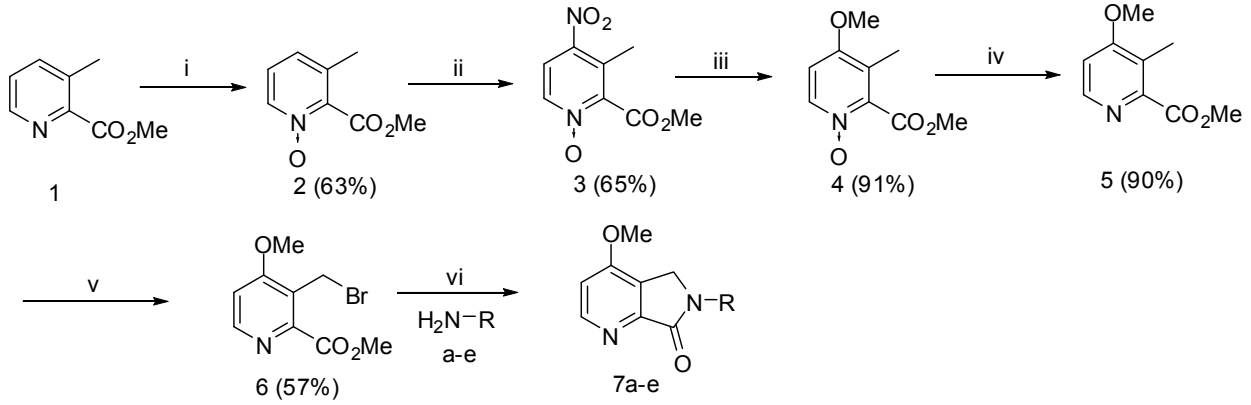
Abstract – A simple and convenient route for the synthesis of a series of 4-methoxy or 5-methoxy substituted 7-aza-isoindolin-1-ones is described. Methoxyl substituted pyridine derivatives were cyclized with different amines under alkaline condition to give the desired products.

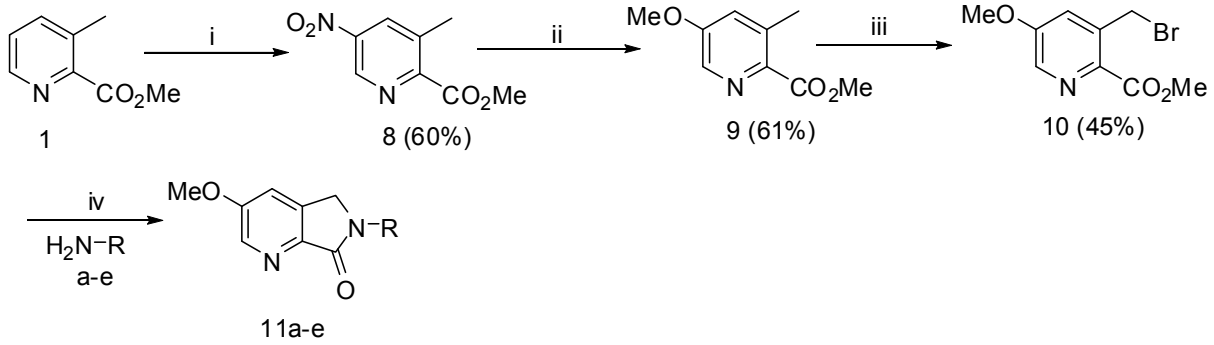
Isoindolinones have a common intermediate skeleton with numerous alkaloids and display various biological properties of pharmaceutical interest.[1-4] Introducing methoxyl group in the aromatic ring of some isoindolinones could not only modulate the bioactivity of these compounds but also provide the opportunity for further chemical modification.[5-7] Although the methoxyl substituted isoindolinones are widely used by biological and synthetic chemists, the synthesis of their aza-analogue derivatives were rarely reported.[8] We describe here a convenient synthetic route for 4-methoxy or 5-methoxy substituted 7-aza-isoindolin-1-ones.

4-Methoxy substituted analogs of 7-aza-isoindolin-1-one were synthesized according to **Scheme 1**. Compound **2** was prepared by the oxidation of **1** with 30% hydrogen peroxide in HOAc. The following nitration of **2** with a mixture of concentrated sulfuric acid and fuming nitric acid could afford **3**.[9] Compound **3** was then treated with K_2CO_3 in methanol to displace the nitro group with methoxy group providing **4**.[10] Compound **5** was given by Pd/C catalyzed hydrogenation reduction. The free radical reaction of *N*-bromosuccinimide (NBS)/azodiisobutyronitrile (AIBN) with **5** could generate **6** in CCl_4 at reflux. Different amines **(a-e)** were cyclized with **6** under alkaline condition to form the final 4-methoxy-7-aza-isoindolinones **7a-e**.[11,12]



Scheme 1. Reagents and conditions: (i) 30% H_2O_2, HOAc, rt to 80 °C. (ii) fuming HNO_3, H_2SO_4, 95-100 °C. (iii) K_2CO_3, MeOH, reflux. (iv) 10% Pd/C, H_2, MeOH, rt. (v) NBS, AIBN, CCl_4, reflux. (vi) K_2CO_3, MeCN, rt to reflux.

5-Methoxy substituted analogs of 7-aza-isoindolin-1-one were synthesized in a similar thinking way (**Scheme 2**). The nitration of **1** with tetrabutylammonium nitrate could involve nitro group on the *meta*-position of pyridine ring.[13,14] Compound **9** was obtained by the methoxylation of **8** in methanol with a stronger base NaOMe. K_2CO_3 was also tried in this case, but no obvious product was generated.



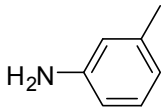
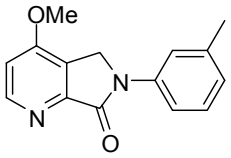
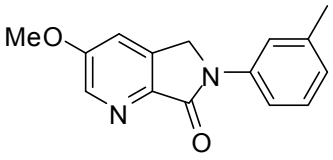
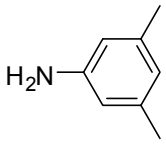
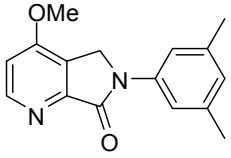
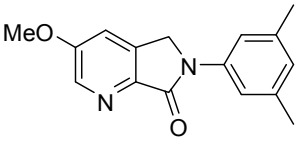
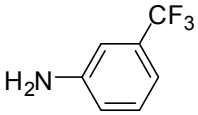
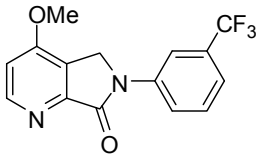
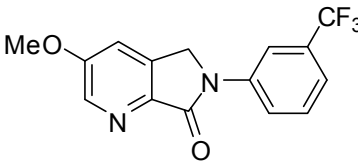
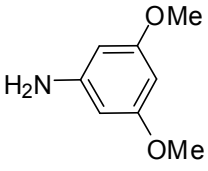
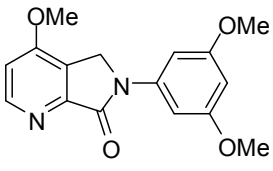
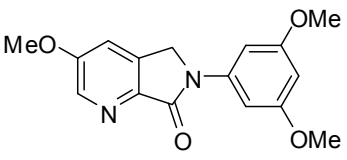
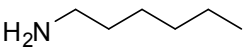
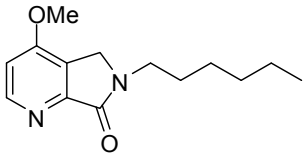
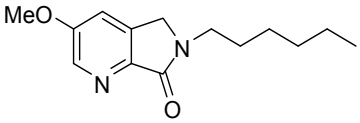
Scheme 2. Reagents and conditions: (i) $Bu_4N^+NO_3^-$, $(CF_3CO)_2O$, CH_2Cl_2, rt. (ii) NaH, MeOH, reflux. (iii) NBS, AIBN, CCl_4, reflux. (iv) K_2CO_3, MeCN, rt to reflux.

The bromomethyl product and the dibromomethyl product were obtained by a ratio of 3:1 when compound **9** (1.0 equiv) was reacted with NBS (1.2 equiv) and AIBN (0.2 equiv) in CCl_4 at reflux. Meanwhile, the bromide **10** was not a stable compound and could slowly turn into black paste at room temperature. Mass spectra of the paste suggested formation of polymeric species, presumably via intermolecular reaction between the nucleophilic pyridine and the benzylic bromide.[15] It was an interesting contrast that the brominated product of compound **5** was mainly the bromide **6**, which was stable; presumably the bulk of the methoxyl group was key to avoiding dibromide and polymerization in

the case.

It was noticed that the yields of **7a-e** and **11a-e** were relevant to the amines used (**Table 1**). The cyclized products of amine **c** were relatively of low yield as compared with other amines, since the nucleophilicity of its amino group was weakened by the trifluoromethyl group on the benzene.

Table 1. Amines (**a-e**) and corresponding methoxyl substituted 7-aza-isoindolinones (**7a-e** and **11a-e**)

Entry	Amines	**7a-e**	Yield (%)	**11a-e**	Yield (%)
a			72%		51%
b			65%		53%
c			40%		36%
d			67%		59%
e			59%		57%

EXPERIMENTAL

Melting points were determined on a SGW X-4 melting point instrument and were uncorrected. ^{1}HNMR and ^{13}C NMR 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 4-methoxy-2-(*m*-tolyl)-7-aza-isoindolin-1-one (7a)

m-Toluidine (140 mg, 1.31 mmol) and K_2CO_3 (90 mg, 0.65 mmol) were added to a solution of methyl 4-methoxy-3-(bromomethyl)picolinate **6** (170 mg, 0.65 mmol) in MeCN (15 mL) under the protection of nitrogen. The resulting mixture was stirred at room temperature for 2 h and then heated to reflux for another 4 h. The reaction mixture was cooled to room temperature, filtered and concentrated in vacuo. The crude residue was purified by column chromatography (100:1 CH_2Cl_2/MeOH) to afford **7a** as a white solid (120 mg, yield 72%, mp 187~188 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.64 (d, 1H, J = 6.0 Hz, NC<u>H</u>), 7.75~7.77 (m, 2H, NCC<u>H</u>), 7.32 (tt, 1H, J = 8.0 Hz, 1.2 Hz, NCCHC<u>H</u>), 7.27 (d, 1H, J = 5.6 Hz, NCHC<u>H</u>), 7.02 (d, 1H, J = 7.2 Hz, NCCHCHC<u>H</u>), 4.9 4(s, 2H, C<u>H</u>$_2$N), 4.01 (s, 3H, CH_3O), 2.36 (s, 3H, CH_3). ^{13}C NMR (400 MHz, DMSO-d_6) δ: 164.8, 161.1, 152.9, 151.1, 139.2, 138.2, 128.8, 125.1, 124.1, 119.8, 116.5, 109.1, 56.1, 45.9, 21.2. ESI-HRMS: calcd for $C_{15}H_{15}N_2O_2$ (MH^+), 255.1134, found 255.1124.

4-Methoxy-2-[3,5--dimethylphenyl]-7-aza-isoindolin-1-one (7b)

7b was afforded by column chromatography (100:1 CH_2Cl_2/MeOH) as a white solid (yield 65%, mp 225~226 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.64 (d, 1H, J = 5.6 Hz, NC<u>H</u>), 7.58 (s, 2H, NCC<u>H</u>), 7.27 (d, 1H, J = 5.6 Hz, NCHC<u>H</u>), 6.85 (s, 1H, CC<u>H</u>C), 4.9 2(s, 2H, C<u>H</u>$_2$N), 4.01 (s, 3H, CH_3O), 2.31 (s, 6H, CH_3). ^{13}C NMR (400 MHz, DMSO-d_6) δ: 164.8, 161.0, 152.8, 151.2, 139.2, 138.0, 125.9, 124.0, 116.9, 109.0, 56.1, 46.0, 21.1. ESI-HRMS: calcd for $C_{16}H_{17}N_2O_2$ (MH^+), 269.1290, found 269.1294.

4-Methoxy-2-[3-(trifluoromethyl)phenyl]-7-aza-isoindolin-1-one (7c)

7c was afforded by column chromatography (200:1 CH_2Cl_2/MeOH) as a white solid (yield 40%, mp 215~216 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.67 (d, 1H, J = 5.6 Hz, NC<u>H</u>), 8.46 (s, 1H, NCC<u>H</u>C), 8.16 (dd, 1H, J = 8.0 Hz, 1.6 Hz, NCC<u>H</u>CH), 7.70 (t, 1H, J = 8.0 Hz, NCCHC<u>H</u>), 7.56 (d, 1H, J = 8.0 Hz, NCCHCHC<u>H</u>), 7.31 (d, 1H, J = 5.6 Hz, NCHC<u>H</u>), 5.06 (s, 2H, C<u>H</u>$_2$N), 4.03 (s, 3H, CH_3O). ^{13}C NMR (400MHz, DMSO-d_6) δ: 165.3, 161.1, 153.0, 150.6, 139.9, 130.2, 129.5~129.8, 122.7~125.4, 124.3, 122.6, 120.6, 115.4, 109.3, 56.1, 46.0. ESI-HRMS: calcd for $C_{15}H_{12}N_2O_2F_3$ (MH^+), 309.0851, found 309.0867.

4-Methoxy-2-(3,5-dimethoxyphenyl)-7-aza-isoindolin-1-one (7d)

7d was afforded by column chromatography (100:1 CH_2Cl_2/MeOH) as a white solid (yield 67%, mp 216~217 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.65 (d, 1H, J = 5.6 Hz, NC<u>H</u>), 7.28 (d, 1H, J = 5.6 Hz, NCHC<u>H</u>), 7.17 (d, 2H, J = 2.4 Hz, NCC<u>H</u>), 6.37 (t, 1H, J =2 .4 Hz, CC<u>H</u>C), 4.95 (s, 2H, C<u>H$_2$</u>N), 4.01 (s, 3H, CH_3O), 3.79 (s, 6H, CH_3O). ^{13}C NMR (400 MHz, DMSO-d_6) δ: 165.0, 161.0, 160.6, 152.9, 151.0, 140.8, 124.0, 109.1, 97.7, 96.4, 56.1, 55.3, 46.1. ESI-HRMS: calcd for $C_{16}H_{17}N_2O_4$ (MH^+), 301.1188, found 301.1201.

4-Methoxy-2-hexyl-7-aza-isoindolin-1-one (7e)

7e was afforded by column chromatography (200:1 CH_2Cl_2/MeOH) as a white solid (yield 59%, mp 96~97 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.65 (d, 1H, J = 5.6 Hz, NC<u>H</u>), 6.89 (d, 1H, J = 5.6 Hz, NCHC<u>H</u>), 4.33 (s, 2H, C<u>H$_2$</u>N), 3.97 (s, 3H, CH_3O), 3.66 (t, 2H, J = 7.2 Hz, NC<u>H$_2$</u>), 1.65~1.70 (m, 2H, NCH$_2$C<u>H$_2$</u>), 1.25~1.38 (m, 6H), 0.88 (t, 3H, J = 6.8 Hz, CH_3). ^{13}C NMR (400 MHz, DMSO-d_6) δ: 165.6, 161.0, 152.4, 151.7, 124.3, 108.4, 55.9, 44.8, 41.9, 30.9, 27.5, 25.9, 22.0, 13.9. ESI-HRMS: calcd for $C_{14}H_{21}N_2O_2$ (MH^+), 249.1603, found 249.1598.

General protocol 5-methoxy-2-(*m*-tolyl)-7-aza-isoindolin-1-one (11a)

m-Toluidine (165 mg, 1.54 mmol) and K_2CO_3 (106 mg, 0.77 mmol) were added to a solution of methyl 5-methoxy-3-(bromomethyl)picolinate **10** (200 mg, 0.77 mmol) in MeCN (15 mL) under the protection of nitrogen. The resulting mixture was stirred at room temperature for 1 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 (100:1 CH_2Cl_2/MeOH) and recrystallized from MeOH to afford **11a** as a yellow solid (100 mg, yield 51%, mp 229~230 °C). ^{1}H NMR (400 Hz, DMSO-d_6) δ: 8.45 (d, 1H, J = 2.4 Hz, NC<u>H</u>), 7.69 (d, 1H, J = 2.8 Hz, CH_3OCC<u>H</u>), 7.72~7.74 (m, 2H, NCC<u>H</u>), 7.32~7.36 (t, 1H, J = 7.6 Hz, NCCHC<u>H</u>), 7.02 (d, 1H, J = 7.6 Hz, CH_3CC<u>H</u>), 4.97 (s, 2H, NC<u>H$_2$</u>), 3.95 (s, 3H, OC<u>H$_3$</u>), 2.37 (s, 3H, CC<u>H$_3$</u>). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 165.0, 157.9, 142.8, 140.6, 139.2, 139.1, 136.0, 129.0, 125.6, 119.9, 116.4, 113.9, 56.1, 48.2, 21.7. ESI-HRMS: calcd for $C_{15}H_{15}N_2O_2$ (MH^+), 255.1134, found 255.1134.

5-Methoxy-2-[3,5-dimethylphenyl]-7-aza-isoindolin-1-one (11b)

11b was afforded by column chromatography (100:1 CH_2Cl_2/MeOH) as a faint yellow solid (yield 53%, mp 271~272 °C). ^{1}H NMR (400 Hz, $CDCl_3$) δ: 8.49 (d, 1H, J = 2.0 Hz, NC<u>H</u>), 7.47 (s, 2H, NCC<u>H</u>), 7.29 (d, 1H, J = 2.0 Hz, CH_3OCC<u>H</u>), 6.84 (s, 1H, NCCC<u>H</u>), 4.78 (s, 2H, NC<u>H$_2$</u>), 3.96 (s, 3H, OC<u>H$_3$</u>), 2.36 (s, 6H, C<u>H$_3$</u>). ^{13}C NMR (400 MHz, $CDCl_3$) δ: 165.0, 157.8, 143.1, 140.6, 139.2, 138.9, 135.8, 126.6, 117.2, 113.9, 56.1, 48.4, 21.6. ESI-HRMS: calcd for $C_{16}H_{17}N_2O_2$ (MH^+), 269.1280, found 269.1290.

5-Methoxy-2-[3-(trifluoromethyl)phenyl]-7-aza-isoindolin-1-one (11c)

11c was afforded by column chromatography (150:1 CH_2Cl_2/MeOH) as a white solid (yield 36%, mp

260~262 °C). ^{1}H NMR (400Hz, DMSO-d_6) δ: 8.48 (d, 1H, J = 2.4 Hz, NC<u>H</u>), 8.43 (s, 1H, NCC<u>H</u>CCF$_3$), 8.10 (d, 1H, J = 8.4 Hz, NCC<u>H</u>), 7.69~7.73 (m, 2H, CF$_3$CC<u>H</u>C<u>H</u>), 7.54 (d, 1H, J = 2.4 Hz, CH$_3$OCC<u>H</u>), 5.08 (s, 2H, NC<u>H</u>$_2$), 3.97 (s, 3H, OC<u>H</u>$_3$). ^{13}C NMR (400MHz, DMSO-d_6) δ: 165.0, 162.3, 157.9, 146.0, 141.4, 140.2~140.6, 138.2, 137.7, 130.2, 120.3~122.3, 120.4, 114.3, 108.2, 56.2, 47.8. ESI-HRMS: calcd for $C_{15}H_{12}N_2O_2F_3$ (MH^+), 309.0851, found 309.0851.

5-Methoxy-2-(3,5-dimethoxyphenyl)-7-aza-isoindolin-1-one (11d)

11d was afforded by column chromatography (50:1 CH_2Cl_2/MeOH) as a yellow solid (yield 59%, mp 218~221 °C). ^{1}H NMR (400Hz, DMSO-d_6) δ: 8.45 (d, 1H, J = 2.4 Hz, NC<u>H</u>), 7.69 (d, 1H, J = 2.4 Hz, CH$_3$OCC<u>H</u>), 7.14 (d, 2H, J = 2.0 Hz, NCC<u>H</u>), 6.37 (t, 1H, J = 2.4 Hz, NCCHCC<u>H</u>), 4.96 (s, 2H, NC<u>H</u>$_2$), 3.95 (s, 3H, OC<u>H</u>$_3$), 3.79 (s, 6H, OC<u>H</u>$_3$). ^{13}C NMR (400 MHz, DMSO-d_6) δ: 164.7, 160.7, 157.7, 141.8, 141.1, 140.3, 137.3, 114.2, 97.6, 95.9, 56.2, 55.2, 48.0. ESI-HRMS: calcd for $C_{16}H_{17}N_2O_4$ (MH^+), 301.1187, found 301.1188.

5-Methoxy-2-hexyl-7-aza-isoindolin-1-one (11e)

11e was afforded by column chromatography (200:1 CH_2Cl_2/MeOH) as a white solid (yield 57%). ^{1}H NMR (400MHz, DMSO-d_6) δ: 8.36 (d, 1H, J = 2.8 Hz, NC<u>H</u>), 7.24 (d, 1H, J = 2.4 Hz, CH$_3$OCC<u>H</u>), 4.31 (s, 2H, NC<u>H</u>$_2$), 3.89 (s, 3H, C<u>H</u>$_3$O), 3.58 (t, 2H, J = 7.2 Hz, NC<u>H</u>$_2$), 1.60~1.64 (m, 2H, NCH$_2$C<u>H</u>$_2$), 1.24~1.37 (m, 6H), 0.82~0.86 (t, 3H, J = 6.8 Hz, CH$_3$). ^{13}C NMR (400 MHz, DMSO-d_6) δ: 166.2, 157.3, 143.3, 139.8, 136.5, 114.2, 56.0, 47.3, 42.8, 31.5, 28.3, 26.5, 22.5, 14.0. ESI-HRMS: calcd for $C_{14}H_{21}N_2O_2$ (MH^+), 249.1603, found 249.1612.

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

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 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 (50:1 CH_2Cl_2/MeOH) to give **2** as paint yellow liquid (3.5 g, yield 63%). ^{1}H NMR (300 MHz, $CDCl_3$): 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>$_3$). MS: *m/z* 168.1 (MH^+).

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

2-(Methyoxycarbonyl)-3-methylpyridine 1-oxide **2** (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 **3** as a faint yellow solid (1.9 g, yield 65%, mp 166~168 °C). ^{1}H NMR (300 MHz, $CDCl_3$): 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>$_3$). MS: *m/z* 213.0 (MH^+).

2-(Methyoxycarbonyl)-3-methyl-4-methoxypyridine 1-oxide (4)

2-(Methyoxycarbonyl)-3-methyl-4-nitropyridine 1-oxide **3** (0.5 g, 2.35 mmol) was dissolved in anhydrous MeOH (20 mL). And potassium carbonate (356 mg, 2.57 mmol) was added to the solution. Then the mixture was heated slowly to reflux and reacted for 2.5 h. When the temperature was cooled down, most of the solvent was removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (50 mL) and washed with water (15 mL). The organic layer was dried (anhydrous Na_2SO_4), concentrated, and purified by chromatography (25:1 CH_2Cl_2/MeOH) to afford **4** as a white solid (423 mg, yield 91%, mp 57~58 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.09 (d, 1H, *J* = 7.2 Hz, NC<u>H</u>), 6.75 (d, 1H, *J* = 7.2 Hz, NCHC<u>H</u>), 4.03 (s, 3H, C<u>H</u>$_3$O), 3.91 (s, 3H, C<u>H</u>$_3$O) , 2.13 (s, 3H, C<u>H</u>$_3$). MS: *m/z* 198.1 (MH^+).

Methyl 4-methoxy-3-methylpicolinate (5)

10% Pd/C (50 mg) was added to a solution of 2-(methyoxycarbonyl)-3-methyl-4-methoxypyridine 1-oxide **4** (423 mg, 2.14 mmol) in MeOH (15 mL) at room temperature. The resulting mixture was stirred under H_2 (1 atm) for 3 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 **5** as a colorless solid (350 mg, yield 90%, mp 52~54 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.43 (d, 1H, *J* = 5.2 Hz, NC<u>H</u>), 6.87 (d, 1H, *J* = 5.2 Hz, NCHC<u>H</u>), 3.97 (s, 3H, C<u>H</u>$_3$O), 3.91 (s, 3H, C<u>H</u>$_3$O), 2.40 (s, 3H, C<u>H</u>$_3$). MS: *m/z* 182.1 (MH^+).

Methyl 4-methoxy-3-(bromomethyl)picolinate (6)

A mixture of methyl 4-methoxy-3-methylpicolinate **5** (265 mg, 1.46 mmol) in CCl_4 (25 mL) with *N*-bromosuccinimide (287 mg, 1.61 mmol) and azodiisobutyronitrile (30 mg, 0.18 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 (pure CH_2Cl_2) to afford **6** as a yellow solid (218 mg, 57%, mp 162~165 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.53 (d, 1H, *J* = 5.7 Hz, NC<u>H</u>), 6.96 (d, 1H, *J* = 5.4 Hz, NCHC<u>H</u>), 4.96 (s, 2H, C<u>H</u>$_2$Br), 4.01 (s, 3H, C<u>H</u>$_3$O), 4.00 (s, 3H, C<u>H</u>$_3$O). MS: *m/z* 261.1 (MH^+).

Methyl 3-methyl-5-nitropicolinate (8)

Trifluoroacetic anhydride (61.2 mL, 0.44 mol) was added dropwise at 0 °C to a solution of methyl 3-methylpicolinate **1** (30.4 g, 0.20 mol) and tetrabutylammonium nitrate (67.0 g, 0.22 mol) in CH_2Cl_2 (500 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 **8** as a white solid (23.4 g, yield 60%, mp 80~82 °C). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.30 (s, 1H, NC<u>H</u>), 8.41 (s, 1H, NCHCC<u>H</u>, 4.02 (s, 3H, C<u>H</u>$_3$O), 2.70(s, 3H, C<u>H</u>$_3$). MS: *m/z* 197.1 (MH^+).

Methyl 5-methoxy-3-methylpicolinate (9)

60% Sodium hydride (6.2 g, 0.15 mol) was dissolved in anhydrous MeOH (500 mL). And methyl 3-methyl-5-nitropicolinate (19.6 g, 0.10 mol) was added to the solution. Then the mixture was heated slowly to reflux and reacted for 2.5 h. When the temperature was cooled down, most of the solvent was removed under reduced pressure. The residue was neutralized with diluted hydrochloric acid to pH=7 and extracted with CH_2Cl_2 (200 mL) for three times. The organic layer was dried (anhydrous Na_2SO_4) and concentrated. The residue was purified by chromatorgraphy (50:1 CH_2Cl_2/MeOH) to afford **9** as a red brown solid (11.0 g, yield 61%, mp 67~69 °C). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.24 (d, 1H, J = 2.8 Hz, NC<u>H</u>), 7.06 (d, 1H, J = 2.4 Hz, CH_3OCC<u>H</u>), 3.96 (s, 3H, C<u>H</u>$_3$O), 3.91 (s, 3H, C<u>H</u>$_3$O), 2.64 (s, 3H, C<u>H</u>$_3$). MS: *m/z* 182.1 (MH^+).

Methyl 5-methoxy-3-(bromomethyl)picolinate (10)

A mixture of methyl 5-methoxy-3-methylpicolinate **9** (362 mg, 2.0 mmol) in CCl_4 (20 mL) with *N*-bromosuccinimide (427 mg, 2.4 mmol) and azodiisobutyronitrile (66 mg, 0.4 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 (pure CH_2Cl_2) to afford **10** as a yellow solid (235 mg, yield 45%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (d, 1H, J = 2.4 Hz, NC<u>H</u>), 7.34 (d, 1H, J = 2.4 Hz, CH_3OCC<u>H</u>), 4.98 (s, 2H, C<u>H</u>$_2$Br), 4.00 (s, 3H, C<u>H</u>$_3$O), 3.95 (s, 3H, C<u>H</u>$_3$O). MS: *m/z* 261.1 (MH^+).

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