

SIMPLE ONE STEP SYNTHESSES OF INDOLE-3-ACETONITRILES FROM INDOLE-3-CARBOXALDEHYDES<sup>1</sup>

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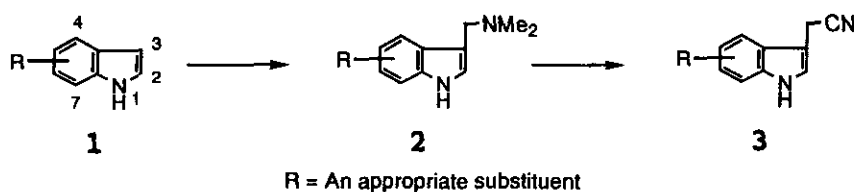
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**Abstract** ——— One step conversion method of indole-3-carboxaldehydes into indole-3-acetonitriles is developed. Applying the method, 4-nitro- (7a), 4-phenyl- (7b), 4-iodo- (7c), 4-methoxy- (7d), and 4-benzyloxyindole-3-acetonitrile (7e) are available in two steps from indole-3-carboxaldehyde (4).

Indole-3-acetonitriles (3) are known not only as plant growth regulators<sup>2</sup> but also as important building blocks for tryptamines and natural products.<sup>3-5</sup> Probably the most common synthesis approach to them is the nucleophilic substitution with cyanide<sup>6</sup> for the dimethylamino group of gramines (2) which are readily obtained by Mannich reaction of indoles (1), as shown in Scheme 1.

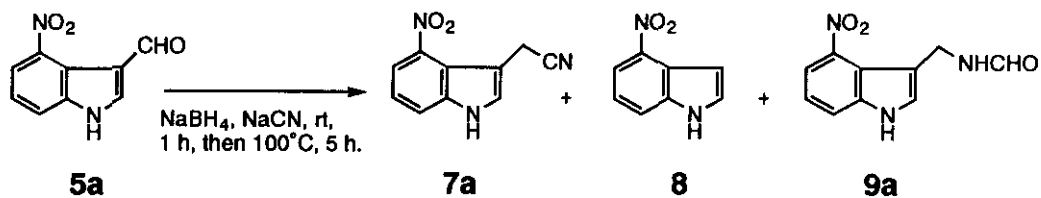
Scheme 1



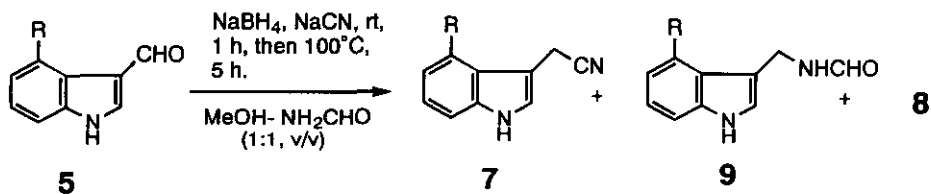
On the other hand, even at present, 4-substituted indole-3-acetonitriles (7, Scheme 2) are difficult to obtain due to the lack of simple preparation method for 4-substituted gramines (6). Our contribution in the indole chemistry has realized one pot syntheses<sup>7</sup> of 4-substituted indole-3-carboxaldehydes (5) from indole-3-carboxaldehyde (4) and a direct conversion of 5 into 6.<sup>8</sup> However, the need of one step method for transforming 5 into 7 is still remained, because the method would easily supply valuable building blocks (7a-e) and consequently provide a short cut for various natural products syntheses such as batzelline C (11),<sup>3</sup> isobatzelline C (12),<sup>3</sup> SF 2140,<sup>4</sup> nephilatoxins (13),<sup>5</sup> and so on. Now, we wish to report the discovery of the desired reaction.

In order to accumulate basic knowledge, we chose 4-nitroindole-3-carboxaldehyde<sup>9</sup> (5a) as a substrate and tested various trials employing cyanating reagents in the presence of reducing agents, such as Me<sub>3</sub>SiCl-



**Table 1**

| Entry | Solvent                             | Yield (%) of |          |           |
|-------|-------------------------------------|--------------|----------|-----------|
|       |                                     | <b>7a</b>    | <b>8</b> | <b>9a</b> |
| 1     | MeOH                                | 36           | 53       | 0         |
| 2     | MeOH-MeNHCHO (1:1, v/v)             | 52           | 27       | 0         |
| 3     | MeOH-DMF (1:1, v/v)                 | 62           | 31       | 0         |
| 4     | NH <sub>2</sub> CHO                 | 61           | 6        | 3         |
| 5     | MeOH-NH <sub>2</sub> CHO (1:1, v/v) | 88           | 2        | 9         |
| 6     | MeOH-NH <sub>2</sub> CHO (1:7, v/v) | 69           | 9        | 5         |

**Table 2**

|          | R                   | Yield (%) of |          |          |
|----------|---------------------|--------------|----------|----------|
|          |                     | <b>7</b>     | <b>9</b> | <b>8</b> |
| <b>a</b> | NO <sub>2</sub>     | 88           | 9        | 2        |
| <b>b</b> | Ph                  | 89           | 5        | 0        |
| <b>c</b> | I                   | 88           | 7        | 0        |
| <b>d</b> | OMe                 | 86           | 11       | 0        |
| <b>e</b> | OCH <sub>2</sub> Ph | 89           | 9        | 0        |
| <b>f</b> | H                   | 95           | 4        | 0        |

indole-3-acetonitriles. Owing to the present method, 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline<sup>3,8</sup> (**10**) is obtained from **4** in three steps and our previous eight steps synthesis of marine alkaloids, batzelline C<sup>3</sup> (**11**) and isobatzelline C (**12**),<sup>3</sup> become shorter by one step (Scheme 2). The present two steps synthesis of 4-benzyloxyindole-3-acetonitrile (**7e**) from **4** could substitute for an expensive four steps synthesis<sup>5</sup> of **7e** from 4-hydroxyindole and would be utilized for the synthetic studies of nephillatoxins such as **13**.<sup>5</sup> 4-Methoxyindole-3-acetonitrile (**7d**), the aglycon of SF 2140,<sup>4</sup> is now available in only two steps from **4** and could be applied for the syntheses of *Mitragyna* alkaloids such as **14**.<sup>11</sup>

The present method is widely applicable for effective syntheses of indole natural products.

## EXPERIMENTAL

Melting points were determined on a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (IR) spectra were determined with a Shimadzu IR-420 spectrophotometer, and proton nuclear magnetic resonance (<sup>1</sup>H-NMR) spectra with a JEOL GSX-500 spectrometer with tetramethylsilane as an internal standard. Mass spectra (MS) were recorded on a JEOL SX-102A spectrometer. Preparative thin-layer chromatography was performed on Merck Kiesel-gel GF<sub>254</sub> (Type 60)(SiO<sub>2</sub>). Column chromatography was performed on silica gel (SiO<sub>2</sub>, 100-200 mesh, from Kanto Chemical Co. Inc.).

**General procedure** ----- NaBH<sub>4</sub> (1.3 mol eq.) was added to a solution of indole-3-carboxaldehyde in MeOH and NH<sub>2</sub>CHO. After stirring at rt for 1 h, NaCN (10 mol eq.) was added to the reaction mixture and the whole was refluxed on oil bath at 100°C for 5 h with stirring. After cooling, brine was added and the whole was extracted with MeOH-CHCl<sub>3</sub> (5:95, v/v). The organic layer was washed with brine, dried over Na<sub>2</sub>SO<sub>4</sub>, and evaporated under reduced pressure to leave the residue, which was column chromatographed on SiO<sub>2</sub> with an appropriate solvent as an eluent.

**4-Nitroindole-3-acetonitrile (7a), 4-nitroindole (8), and N-(4-nitroindol-3-yl)methylformamide (9a) from 4-nitroindole-3-carboxaldehyde (5a): Table 1, Entry 5** ----- In the general procedure, 23.4 mg (0.619 mmol) of NaBH<sub>4</sub>, 86.0 mg (0.453 mmol) of **5a**,<sup>7g</sup> 4 mL of MeOH and 4 mL of NH<sub>2</sub>CHO, 230.5 mg (4.70 mmol) of NaCN were used. The residue was column chromatographed on SiO<sub>2</sub> with CHCl<sub>3</sub> and then MeOH-CHCl<sub>3</sub> (5:95, v/v) as an eluent to give **8** (1.8 mg, 2%) as the early part of the fractions. From the middle part, **7a** (80.0 mg, 88%) was obtained. From the later part, **9a** (8.5 mg, 9%) was obtained. **7a** and **8** are identical with the authentic samples prepared according to our procedures.<sup>9,10</sup> **9a**: mp 224.0-225.0°C (yellow needles, recrystallized from MeOH). IR (KBr): 3330, 3270, 1623, 1509, 1317 cm<sup>-1</sup>. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, 27°C, rotational isomers existed) δ: 4.53 (16/9H, d, J=5.4 Hz), 4.57 (2/9H, d, J=6.1 Hz), 7.28 (1H, t, J=8.1 Hz), 7.61 (1/9H, d, J=2.2 Hz), 7.63 (8/9H, d, J=2.2 Hz), 7.83 (8/9H, dd, J=8.1 and 1.0 Hz), 7.84 (1/9H, dd, J=8.1 and 1.0 Hz), 7.86 (1/9H, dd, J=8.1 and 1.0 Hz), 7.88 (8/9H, dd, J=8.1 and 1.0 Hz), 8.00 (8/9H, dt, J=2.0 and 1.0 Hz), 8.06 (1/9H, d, J=11.7 Hz), 8.16 (1H, br s, disappeared on addition of D<sub>2</sub>O), 11.88 (1H,

br s, disappeared on addition of D<sub>2</sub>O). MS *m/z* : 219 (M<sup>+</sup>). *Anal.* Calcd for C<sub>10</sub>H<sub>9</sub>N<sub>3</sub>O<sub>3</sub>: C, 54.79; H, 4.14; N, 19.17. Found: C, 54.70; H, 4.15; N, 19.08.

**4-Phenylindole-3-acetonitrile (7b) and N-(4-phenylindol-3-yl)methylformamide (9b) from 4-phenylindole-3-carboxaldehyde (5b) -----** In the general procedure, 22.6 mg (0.597 mmol) of NaBH<sub>4</sub>, 102.8 mg (0.465 mmol) of **5b**, <sup>7b,d</sup> 4 mL of MeOH and 4 mL of NH<sub>2</sub>CHO, 230.8 mg (4.71 mmol) of NaCN were used. The residue was column chromatographed on SiO<sub>2</sub> with CHCl<sub>3</sub> and then MeOH-CHCl<sub>3</sub> (5:95, v/v) as an eluent to give **7b** (96.1 mg, 89%) as the early part of the fractions. From the later part, **9b** (5.6 mg, 5%) was obtained. **7b**: colorless oil. IR (film): 3380, 3320, 2250, 1611, 1484, 1411, 1335 cm<sup>-1</sup>. <sup>1</sup>H-NMR (CDCl<sub>3</sub>) δ: 3.25 (2H, d, *J*=1.2 Hz), 7.03 (1H, dd, *J*=7.2 and 1.0 Hz), 7.27 (1H, dd, *J*=8.1 and 7.2 Hz), 7.31 (1H, dt, *J*=2.4 and 1.2 Hz), 7.39-7.48 (6H, m), 8.32 (1H, br s). High resolution MS *m/z*: Calcd for C<sub>16</sub>H<sub>12</sub>N<sub>2</sub>: 232.1001. Found: 232.1000. **9b**: mp 197.0-198.0°C (colorless leaves, recrystallized from MeOH). IR (KBr): 3270, 3150, 1631, 1532, 1355 cm<sup>-1</sup>. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, 27°C, rotational isomers existed) δ: 3.86 (14/8H, d, *J*=5.4 Hz), 3.94 (2/8H, d, *J*=6.1 Hz), 6.82 (7/8H, dd, *J*=7.1 and 1.0 Hz), 6.84 (1/8H, dd, *J*=7.1 and 1.0 Hz), 7.13 (7/8H, dd, *J*=8.1 and 7.1 Hz), 7.14 (1/8H, dd, *J*=8.1 and 7.1 Hz), 7.23 (7/8H, dt, *J*=2.4 and 1.2 Hz), 7.25 (1/8H, s), 7.34-7.48 (50/8H, m), 7.86 (7/8H, s), 7.87 (7/8H, br s, disappeared on addition of D<sub>2</sub>O), 11.16 (7/8H, br s, disappeared on addition of D<sub>2</sub>O), 11.19 (1/8H, br s, disappeared on addition of D<sub>2</sub>O). MS *m/z*: 250 (M<sup>+</sup>). *Anal.* Calcd for C<sub>16</sub>H<sub>14</sub>N<sub>2</sub>O: C, 76.78; H, 5.64; N, 11.19. Found: C, 76.62; H, 5.60; N, 11.15.

**4-Iodoindole-3-acetonitrile (7c) and N-(4-iodoindol-3-yl)methylformamide (9c) from 4-iodoindole-3-carboxaldehyde (5c) -----** In the general procedure, 21.0 mg (0.555 mmol) of NaBH<sub>4</sub>, 121.0 mg (0.447 mmol) of **5c**, <sup>7a,c</sup> 4 mL of MeOH and 4 mL of NH<sub>2</sub>CHO, 226.0 mg (4.61 mmol) of NaCN were used. The residue was column chromatographed on SiO<sub>2</sub> with MeOH-CHCl<sub>3</sub> (1:99, v/v) and then MeOH-CHCl<sub>3</sub> (5:95, v/v) as an eluent to give **7c** (111.3 mg, 88%) as the early part of the fractions. From the later part, **9c** (9.9 mg, 7%) was obtained. **7c** is identical with the authentic samples prepared according to our procedures.<sup>9</sup> **9c**: mp 207.0-209.0°C (colorless needles, recrystallized from MeOH). IR (KBr): 3270, 3120, 1628, 1532, 1353 cm<sup>-1</sup>. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, 27°C, rotational isomers existed) δ: 4.65 (20/11H, d, *J*=5.4 Hz), 4.74 (2/11H, d, *J*=5.9 Hz), 6.83 (1H, dd, *J*=8.1 and 7.6 Hz), 7.32 (1/11H, d, *J*=2.2 Hz), 7.37 (10/11H, d, *J*=2.7 Hz), 7.42 (1H, dd, *J*=8.1 and 1.0 Hz), 7.46 (1/11H, dd, *J*=7.6 and 1.0 Hz), 7.47 (10/11H, dd, *J*=7.6 and 1.0 Hz), 7.86 (1/11H, br s, disappeared on addition of D<sub>2</sub>O), 8.07 (10/11H, dt, *J*=2.0 and 1.0 Hz), 8.17 (1/11H, d, *J*=11.7 Hz), 8.21 (10/11H, br s, disappeared on addition of D<sub>2</sub>O), 11.28 (1H, br s, disappeared on addition of D<sub>2</sub>O). MS *m/z*: 300 (M<sup>+</sup>). *Anal.* Calcd for C<sub>10</sub>H<sub>9</sub>IN<sub>2</sub>O: C, 40.02; H, 3.02; N, 9.33. Found: C, 40.06; H, 2.99; N, 9.09.

**4-Methoxyindole-3-acetonitrile (7d) and N-(4-methoxyindol-3-yl)methylformamide (9d) from 4-methoxyindole-3-carboxaldehyde (5d) -----** In the general procedure, 23.0 mg

(0.608 mmol) of  $\text{NaBH}_4$ , 80.4 mg (0.459 mmol) of **5d**,<sup>7a</sup> 4 mL of MeOH and 4 mL of  $\text{NH}_2\text{CHO}$ , 223.8 mg (4.57 mmol) of NaCN were used. The residue was column chromatographed on  $\text{SiO}_2$  with  $\text{CHCl}_3$  as an eluent to give **7d** (73.5 mg, 86%) as the early part of the fractions. From the later part, **9d** (10.2 mg, 11%) was obtained. **7d**: mp 145.0-146.0°C (colorless prisms, recrystallized from  $\text{CHCl}_3$ -hexane). IR (KBr): 3360, 2270, 1617, 1590, 1509, 1355, 1260, 1091, 752, 733  $\text{cm}^{-1}$ .  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 3.92 (3H, s), 4.05 (2H, d,  $J=1.1$  Hz), 6.50 (1H, d,  $J=8.0$  Hz), 6.96 (1H, d,  $J=8.0$  Hz), 7.09 (1H, dt,  $J=2.2$  and 1.1 Hz), 7.12 (1H, t,  $J=8.0$  Hz), 8.08 (1H, br s, disappeared on addition of  $\text{D}_2\text{O}$ ). MS  $m/z$ : 186 ( $\text{M}^+$ ). Anal. Calcd for  $\text{C}_{11}\text{H}_{10}\text{N}_2\text{O}$ : C, 70.95; H, 5.41; N, 15.04. Found: C, 70.98; H, 5.41; N, 15.11. **9d**: mp 190.0-192.0°C (colorless prisms, recrystallized from MeOH). IR (KBr): 3230, 3180, 1635, 1354  $\text{cm}^{-1}$ .  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ , 27°C, rotational isomers existed)  $\delta$ : 3.84 (3H, s), 4.49 (2/6H, d,  $J=6.1$  Hz), 4.51 (10/6H, d,  $J=5.6$  Hz), 6.46 (1H, dd,  $J=7.6$  and 0.7 Hz), 6.93 (5/6H, dd,  $J=8.1$  and 1.0 Hz), 6.94 (1/6H, dd,  $J=8.1$  and 1.0 Hz), 6.98 (5/6H, dd,  $J=8.1$  and 7.6 Hz), 6.99 (1/6H, dd,  $J=8.1$  and 7.6 Hz), 7.06 (1H, d,  $J=2.4$  Hz), 7.72 (1/6H, br s, disappeared on addition of  $\text{D}_2\text{O}$ ), 8.04 (5/6H, d,  $J=1.7$  Hz), 8.05 (5/6H, br s, disappeared on addition of  $\text{D}_2\text{O}$ ), 8.12 (1/6H, d,  $J=11.7$  Hz), 10.88 (5/6H, br s, disappeared on addition of  $\text{D}_2\text{O}$ ), 10.90 (1/6H, br s, disappeared on addition of  $\text{D}_2\text{O}$ ). MS  $m/z$ : 204 ( $\text{M}^+$ ). Anal. Calcd for  $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}_2 \cdot 1/8\text{H}_2\text{O}$ : C, 63.99; H, 5.98; N, 13.57. Found: C, 63.91; H, 5.87; N, 13.33.

**4-Benzoyloxyindole-3-acetonitrile (7e) and N-(4-methoxyindol-3-yl)methylformamide (9e) from 4-benzoyloxyindole-3-carboxaldehyde (5e)** ----- In the general procedure, 26.2 mg (0.693 mmol) of  $\text{NaBH}_4$ , 111.0 mg (0.442 mmol) of **5e**,<sup>7a</sup> 4 mL of MeOH and 4 mL of  $\text{NH}_2\text{CHO}$ , 222.7 mg (4.54 mmol) of NaCN were used. The residue was column chromatographed on  $\text{SiO}_2$  with  $\text{CHCl}_3$  and then MeOH- $\text{CHCl}_3$  (5:95, v/v) as an eluent to give **7e** (102.8 mg, 89%) as the early part of the fractions. From the later part, **9e** (11.2 mg, 9%) was obtained. **7e**: mp 84.0-86.0°C (colorless needles, recrystallized from benzene). IR (KBr): 3380, 2260, 1616, 1590, 1507, 1261  $\text{cm}^{-1}$ .  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ )  $\delta$ : 4.02 (2H, d,  $J=1.2$  Hz), 5.18 (2H, s), 6.59 (1H, d,  $J=7.8$  Hz), 6.99 (1H, d,  $J=8.1$  Hz), 7.11 (1H, dd,  $J=8.1$  and 7.8 Hz), 7.12 (1H, dt,  $J=2.4$  and 1.2 Hz), 7.35 (1H, br t,  $J=7.3$  Hz), 7.42 (2H, br t,  $J=7.3$  Hz), 7.49 (2H, br d,  $J=7.3$  Hz), 8.12 (1H, br s). MS  $m/z$ : 262 ( $\text{M}^+$ ). Anal. Calcd for  $\text{C}_{17}\text{H}_{14}\text{N}_2\text{O}$ : C, 77.84; H, 5.38; N, 10.68. Found: C, 77.83; H, 5.39; N, 10.37. **9e**: colorless oil. IR (film): 3370, 3260, 1661, 1502, 1260  $\text{cm}^{-1}$ .  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ , 27°C, rotational isomers existed)  $\delta$ : 4.51 (2/7H, d,  $J=6.1$  Hz), 4.54 (12/7H, d,  $J=5.4$  Hz), 5.20 (2H, s), 6.54-6.59, (1H, m), 6.94-6.99 (2H, m), 7.06 (1/7H, d,  $J=2.4$  Hz), 7.08 (6/7H, d,  $J=2.4$  Hz), 7.29-7.43 (3H, m), 7.52 (2H, br d,  $J=7.6$  Hz), 7.70 (1/7H, br s, disappeared on addition of  $\text{D}_2\text{O}$ ), 7.96 (1/7H, d,  $J=11.7$  Hz), 8.02 (6/7H, dt,  $J=2.0$  and 1.0 Hz), 8.08 (6/7H, br s, disappeared on addition of  $\text{D}_2\text{O}$ ), 10.93 (1H, br s, disappeared on addition of  $\text{D}_2\text{O}$ ). High resolution MS  $m/z$ : Calcd for  $\text{C}_{17}\text{H}_{16}\text{N}_2\text{O}_2$ : 280.1212. Found: 280.1208.

**Indole-3-acetonitrile (7f) and N-(indol-3-yl)methylformamide (9f) from indole-3-car-**

**boxaldehyde (5f)** ----- In the general procedure, 23.4 mg (0.619 mmol) of NaBH<sub>4</sub>, 68.4 mg (0.472 mmol) of **5f**, 4 mL of MeOH and 4 mL of NH<sub>2</sub>CHO, 237.0 mg (4.84 mmol) of NaCN were used. The residue was column chromatographed on SiO<sub>2</sub> with CHCl<sub>3</sub> and then MeOH-CHCl<sub>3</sub> (5:95, v/v) as an eluent to give **7f** (70.1 mg, 95%) as the early part of the fractions. From the later part, **9f** (3.6 mg, 4%) was obtained. **7f** was identical with the commercially available sample. **9f** colorless oil. IR (film): 3370, 3260, 1656 cm<sup>-1</sup>. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, 27°C, rotational isomers existed) δ: 4.42 (2/10H, d, *J*=5.9 Hz), 4.43 (18/10H, d, *J*=5.9 Hz), 6.99 (9/10H, ddd, *J*=8.1, 7.1, and 1.0 Hz), 7.00 (1/10H, ddd, *J*=8.1, 7.1, and 1.0 Hz), 7.08 (9/10H, ddd, *J*=8.1, 7.1, and 1.0 Hz), 7.09 (1/10H, ddd, *J*=8.1, 7.1, and 1.0 Hz), 7.24 (1/10H, d, *J*=2.4 Hz), 7.26 (9/10H, d, *J*=2.4 Hz), 7.35 (9/10H, dt, *J*=8.1 and 1.0 Hz), 7.36 (1/10H, dt, *J*=8.1 and 1.0 Hz), 7.54 (9/10H, br d, *J*=8.1 Hz), 7.56 (1/10H, br d, *J*=8.1 Hz), 8.04 (1/10H, br s, disappeared on addition of D<sub>2</sub>O), 8.06 (9/10H, dt, *J*=2.0 and 1.0 Hz), 8.21 (1/10H, d, *J*=11.7 Hz), 8.25 (9/10H, br s, disappeared on addition of D<sub>2</sub>O), 10.91 (1H, br s, disappeared on addition of D<sub>2</sub>O). High resolution MS *m/z*: Calcd for C<sub>10</sub>H<sub>10</sub>N<sub>2</sub>O: 174.0793. Found: 174.0793.

**N-(4-Nitroindol-3-yl)methylformamide (9a) from 4-nitroindole-3-carboxaldehyde (5a)** ----- In the general procedure, 25.0 mg (0.661 mmol) of NaBH<sub>4</sub>, 86.0 mg (0.453 mmol) of **5a**, 4 mL of MeOH, and 4 mL of NH<sub>2</sub>CHO were used. After stirring at room temperature for 1 h, the whole was refluxed on oil bath at 100°C for an additional 12 h with stirring. The residue was recrystallized from MeOH to afford **9a** as yellow needles (50.3 mg). Mother liquor was purified by column chromatography on SiO<sub>2</sub> with CHCl<sub>3</sub> and then MeOH-CHCl<sub>3</sub> (5:95, v/v) as an eluent to give **8** (3.2 mg, 4%) as the early part of the fractions. From the later part, **9a** (24.2 mg) was obtained. Total yield of **9a** was 74.5 mg (75%).

Similar experiments starting from **5b-f** afforded **9b-f** in 68, 72, 57, 62, and 64% yields, respectively.

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