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SIMPLE ONE STEP SYNTHESSES OF INDOLE-3-ACETONITRILES FROM INDOLE-3-CARBOXALDEHYDES¹

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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 regulators² but also as important building blocks for tryptamines and natural products.³⁻⁵ Probably the most common synthesis approach to them is the nucleophilic substitution with cyanide⁶ 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 syntheses⁷ of 4-substituted indole-3-carboxaldehydes (5) from indole-3-carboxaldehyde (4) and a direct conversion of 5 into 6.⁸ 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),³ isobatzelline C (12),³ SF 2140,⁴ nephilatoxins (13),⁵ 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-carboxaldehyde⁹ (5a) as a substrate and tested various trials employing cyanating reagents in the presence of reducing agents, such as Me₃SiCl-

NaI-KCN-Et₃SiH, Me₃SiCl-NaI-KCN-NaBH₄, Me₃SiCN-NaBH₄, and so on. During these studies,⁸ we observed that simple treatment of **5a** sequentially with NaBH₄, and then with NaCN in MeOH, produced 4-nitroindole-3-acetonitrile⁹ (**7a**) and 4-nitroindole^{9,10} (**8**). Based on the finding, further examinations of the reaction conditions were carried out, and the combination of about 1.3 mol eq. of NaBH₄ and about 10 mol eq. of NaCN was found to be suitable for our purposes as shown in Table 1 (Entry 1), affording **7a** and **8** in 36 and 53% yields, respectively. Furthermore, when the solvent was changed to MeOH-MeNHCHO (1:1, v/v), the yield of **7a** increased slightly (Entry 2). Change in solvent to MeOH-DMF (1:1, v/v) increased the yield of **7a** to 62% (Entry 3). It is interesting to note that NH₂CHO dramatically suppressed the formation of **8** and the yield of **7a** was improved (Entry 4) in comparison with the results of Entries 1 and 2. Therefore, various mixed solvents using MeOH and NH₂CHO were examined and finally 1:1 mixture of MeOH-NH₂CHO was found to be a solvent of choice, producing **7a** in 88% yield together with *N*-(4-nitroindol-3-yl)methylformamide (**9a**) as a by-product in 9% yield (Entry 5). When the same reaction was carried out without NaCN, **9a** was exclusively produced in 75% yield together with 4% yield of **8**. Under similar reaction conditions, **9 b-f** were prepared in 68, 72, 57, 62, and 64% yields, respectively.

Scheme 2

Employing the above reaction conditions, various indole-3-acetonitriles (**7b-f**) having phenyl, halogen, oxygen functional groups, were obtained in excellent to good yields as shown in Table 2 in one step from the corresponding indole-3-carboxaldehydes (**5b-f**) together with a small amount of **9 b-f**, respectively.

Thus, we succeeded in developing a simple one step conversion method of indole-3-carboxaldehydes into

Table 1

Entry	Solvent	Yield (%) of		
		7a	8	9a
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 ₂ CHO	61	6	3
5	MeOH-NH ₂ CHO (1:1, v/v)	88	2	9
6	MeOH-NH ₂ CHO (1:7, v/v)	69	9	5

Table 2

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

indole-3-acetonitriles. Owing to the present method, 1,3,4,5-tetrahydropyrrolo[4,3,2-*de*]quinoline^{3,8} (**10**) is obtained from **4** in three steps and our previous eight steps synthesis of marine alkaloids, batzelline C³ (**11**) and isobatzelline C (**12**),³ 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 synthesis⁵ of **7e** from 4-hydroxyindole and would be utilized for the synthetic studies of nephillatoxins such as **13**.⁵ 4-Methoxyindole-3-acetonitrile (**7d**), the aglycon of SF 2140,⁴ is now available in only two steps from **4** and could be applied for the syntheses of Mitragyna alkaloids such as **14**.¹¹ 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 (¹H-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 GF₂₅₄ (Type 60)(SiO₂). Column chromatography was performed on silica gel (SiO₂, 100-200 mesh, from Kanto Chemical Co. Inc.).

General procedure ----- NaBH₄ (1.3 mol eq.) was added to a solution of indole-3-carboxaldehyde in MeOH and NH₂CHO. 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-CHCl₃ (5:95, v/v). The organic layer was washed with brine, dried over Na₂SO₄, and evaporated under reduced pressure to leave the residue, which was column chromatographed on SiO₂ 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 NaBH₄, 86.0 mg (0.453 mmol) of **5a**,^{7g} 4 mL of MeOH and 4 mL of NH₂CHO, 230.5 mg (4.70 mmol) of NaCN were used. The residue was column chromatographed on SiO₂ with CHCl₃ and then MeOH-CHCl₃ (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.^{9,10} **9a**: mp 224.0-225.0°C (yellow needles, recrystallized from MeOH). IR (KBr): 3330, 3270, 1623, 1509, 1317 cm⁻¹. ¹H-NMR (DMSO-d₆, 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 D₂O), 11.88 (1H,

br s, disappeared on addition of D₂O). MS *m/z* : 219 (M⁺). *Anal.* Calcd for C₁₀H₉N₃O₃: 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 NaBH₄, 102.8 mg (0.465 mmol) of **5b**, ^{7b,d} 4 mL of MeOH and 4 mL of NH₂CHO, 230.8 mg (4.71 mmol) of NaCN were used. The residue was column chromatographed on SiO₂ with CHCl₃ and then MeOH-CHCl₃ (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⁻¹. ¹H-NMR (CDCl₃) 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 C₁₆H₁₂N₂: 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⁻¹. ¹H-NMR (DMSO-d₆, 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 D₂O), 11.16 (7/8H, br s, disappeared on addition of D₂O), 11.19 (1/8H, br s, disappeared on addition of D₂O). MS *m/z*: 250 (M⁺). *Anal.* Calcd for C₁₆H₁₄N₂O: 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 NaBH₄, 121.0 mg (0.447 mmol) of **5c**, ^{7a,c} 4 mL of MeOH and 4 mL of NH₂CHO, 226.0 mg (4.61 mmol) of NaCN were used. The residue was column chromatographed on SiO₂ with MeOH-CHCl₃ (1:99, v/v) and then MeOH-CHCl₃ (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.⁹ **9c**: mp 207.0-209.0°C (colorless needles, recrystallized from MeOH). IR (KBr): 3270, 3120, 1628, 1532, 1353 cm⁻¹. ¹H-NMR (DMSO-d₆, 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 D₂O), 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 D₂O), 11.28 (1H, br s, disappeared on addition of D₂O). MS *m/z*: 300 (M⁺). *Anal.* Calcd for C₁₀H₉IN₂O: 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 NaBH_4 , 80.4 mg (0.459 mmol) of **5d**, ^{7a} 4 mL of MeOH and 4 mL of NH_2CHO , 223.8 mg (4.57 mmol) of NaCN were used. The residue was column chromatographed on SiO_2 with 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 CHCl_3 -hexane). IR (KBr): 3360, 2270, 1617, 1590, 1509, 1355, 1260, 1091, 752, 733 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 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 D_2O). MS m/z : 186 (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 cm^{-1} . $^1\text{H-NMR}$ (DMSO-d_6 , 27°C, rotational isomers existed) δ : 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 D_2O), 8.04 (5/6H, d, $J=1.7$ Hz), 8.05 (5/6H, br s, disappeared on addition of D_2O), 8.12 (1/6H, d, $J=11.7$ Hz), 10.88 (5/6H, br s, disappeared on addition of D_2O), 10.90 (1/6H, br s, disappeared on addition of D_2O). MS m/z : 204 (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-Benzyloxyindole-3-acetonitrile (7e) and N-(4-methoxyindol-3-yl)methylformamide (9e) from 4-benzyloxyindole-3-carboxaldehyde (5e) -----

In the general procedure, 26.2 mg (0.693 mmol) of NaBH_4 , 111.0 mg (0.442 mmol) of **5e**, ^{7a} 4 mL of MeOH and 4 mL of NH_2CHO , 222.7 mg (4.54 mmol) of NaCN were used. The residue was column chromatographed on SiO_2 with CHCl_3 and then MeOH- 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 cm^{-1} . $^1\text{H-NMR}$ (CDCl_3) δ : 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 (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 cm^{-1} . $^1\text{H-NMR}$ (DMSO-d_6 , 27°C, rotational isomers existed) δ : 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 D_2O), 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 D_2O), 10.93 (1H, br s, disappeared on addition of D_2O). 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 NaBH₄, 68.4 mg (0.472 mmol) of **5 f**, 4 mL of MeOH and 4 mL of NH₂CHO, 237.0 mg (4.84 mmol) of NaCN were used. The residue was column chromatographed on SiO₂ with CHCl₃ and then MeOH-CHCl₃ (5:95, v/v) as an eluent to give **7 f** (70.1 mg, 95%) as the early part of the fractions. From the later part, **9 f** (3.6 mg, 4%) was obtained. **7 f** was identical with the commercially available sample. **9 f**: colorless oil. IR (film): 3370, 3260, 1656 cm⁻¹. ¹H-NMR (DMSO-d₆, 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 D₂O), 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 D₂O), 10.91 (1H, br s, disappeared on addition of D₂O). High resolution MS *m/z*: Calcd for C₁₀H₁₀N₂O: 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 NaBH₄, 86.0 mg (0.453 mmol) of **5a**, 4 mL of MeOH, and 4 mL of NH₂CHO 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 SiO₂ with CHCl₃ and then MeOH-CHCl₃ (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 **5 b-f** afforded **9 b-f** in 68, 72, 57, 62, and 64% yields, respectively.

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