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Condensed Heteroaromatic Ring Systems. VI.[1] Synthesis of Indoles and Pyrrolopyridines from *o*-Nitroarylacetylenes

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Catalytic hydrogenation of *o*-nitrophenylacetaldehyde diethyl acetal over palladium–carbon, followed by intramolecular cyclization of the resulting *o*-aminophenylacetaldehyde diethyl acetal with hydrochloric acid, gave indole. Similarly, 4-methylindole, ethyl 5-indolecarboxylate, and various pyrrolopyridines were synthesized from the corresponding *o*-nitroacrylacetaldehyde derivatives. The preparation of the desired *o*-nitroarylacetaldehydes was accomplished by the condensation of *o*-halonitroaromatics with trimethylsilylacetylene in the presence of dichlorobis(triphenylphosphine)palladium as a catalyst, followed by ethanolysis of the resulting *o*-(trimethylsilylethynyl)nitroaromatics.

Keywords——*o*-halonitroaromatic; *o*-cyanohaloaromatic; trimethylsilylacetylene; palladium-catalyzed reaction; cyclization; indole; pyrrolopyridine

The reduction of *o*-nitrobenzyl ketones (**1**) with a variety of reagents gives 2-substituted indole derivatives (**3**) through the spontaneous cyclization of the intermediate *o*-aminobenzyl ketones (**2**). This reaction is known as the Baeyer–Jackson indole synthesis.[2]

It has also been reported that various aryl halides, including halo-*N*-heteroaromatics, smoothly react with trimethylsilylacetylene (TMSA) in the presence of dichlorobis(triphenylphosphine)palladium to form the corresponding trimethylsilylethynyl derivatives,[3] and that the trimethylsilylethynyl group introduced into the π-electron-deficient heteroaromatic rings is convertible to a 2,2-dimethoxyethyl group usually, or a 2-methoxyethenyl group in some cases.[4]

From these points of view, our interest was focused on modification of the Baeyer–Jackson indole synthesis. The present paper deals with a facile indole synthesis from *o*-bromonitrobenzene derivatives. The method is also applicable to the synthesis of pyrrolopyridines from *o*-halonitropyridines.

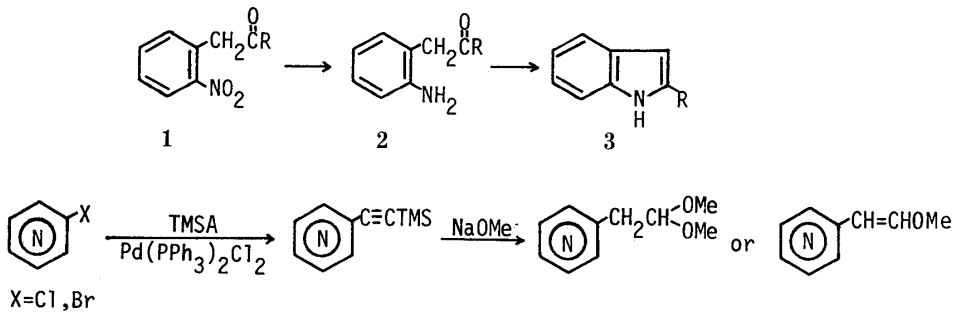


Chart 1

Firstly, synthesis of indole was investigated. The reaction of 2-bromonitrobenzene (**4a**) with TMSA under the reported conditions,[3] followed by heating with sodium ethoxide in

ethanol, gave 2-(2,2-diethoxyethyl)nitrobenzene (**5**), as expected. Catalytic hydrogenation of **5** over palladium–carbon gave 2-(2,2-diethoxyethyl)aniline (**6**) in quantitative yield. When **6** was treated with concentrated hydrochloric acid in ethanol, indole (**7a**) was obtained in 34% overall yield from **4a**. Compound **7a** was identical with an authentic specimen of indole. Although 4-methylindole (**7b**) was obtained from 2-bromo-3-methylnitrobenzene (**4b**) in essentially the same manner, the reaction pathway is slightly different from that to **7a**. Namely, the product obtained from the reaction of **4b** with TMSA was treated with sodium ethoxide to afford 2-(2-ethoxyethenyl)-3-methylnitrobenzene (**8**). In order to transform the enol ether group in **8** to a stable form for catalytic hydrogenation, **8** was treated with ethylene glycol under acidic conditions to yield 2-methyl-6-nitrophenylacetaldehyde ethylene acetal (**9**), which was then converted into **7b** by catalytic hydrogenation of its nitro group and subsequent cyclization.

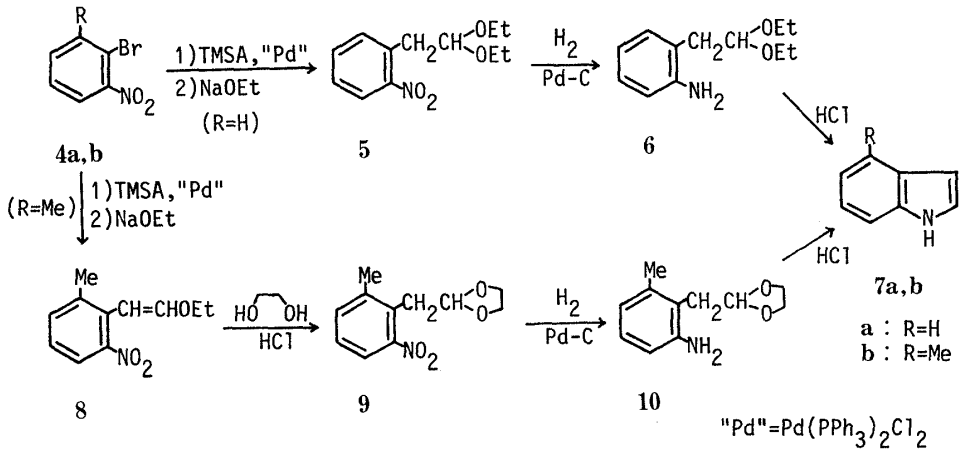


Chart 2

Indole derivatives containing an appropriate carbon functional group at the 4-position are considered to be favorable intermediates for the synthesis of some ergot alkaloids. Thus, the synthesis of ethyl 4-indolecarboxylate (**17**), as a representative of such indole derivatives, was accomplished through the route shown in Chart 3. In contrast to the above results, when ethyl 3-nitro-2-(trimethylsilylethynyl)benzoate (**12**), derived from ethyl 2-bromo-3-nitrobenzoate (**11**), was reacted with sodium ethoxide, the lactone (**13**) was obtained. The formation of **13** can be reasonably explained by the participation of the neighboring ethoxycarbonyl group in the expected compound (**14**). The cyclic intermediate (**15**) may be sub-

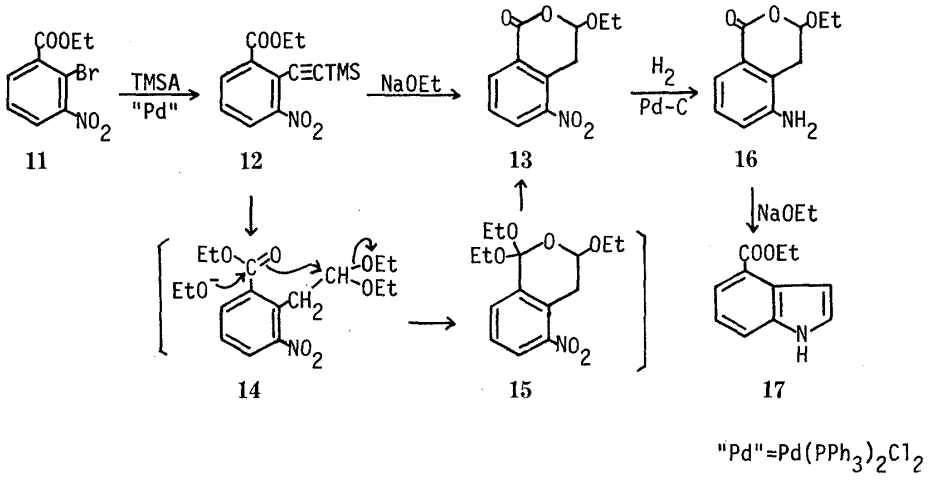


Chart 3

jected to hydrolysis to give **13**. Catalytic hydrogenation of **13** over palladium–carbon gave the aminolactone (**16**), which was treated with sodium ethoxide at room temperature to afford ethyl 4-indolecarboxylate (**17**).

Secondly, in order to estimate the scope and limitations of our reaction, synthesis of pyrrolopyridines from *o*-halonitropyridine derivatives was investigated. Namely, 4-iodo-2,6-dimethyl-3-nitropyridine (**18**) was allowed to react with TMSA, and then the corresponding trimethylsilylethynyl compound was converted to the acetal (**19**). Catalytic hydrogenation of **19** gave 3-amino-4-(2,2-diethoxyethyl)-2,6-dimethylpyridine (**20**). Like **6**, the aminoacetal (**20**) underwent cyclization, and 5,7-dimethylpyrrolo[2,3-*c*]pyridine (**21**) was obtained, as expected. Similarly, unsubstituted pyrrolo[3,2-*b*]pyridine (**25**) was readily synthesized from 2-chloro-3-nitropyridine (**22**). On the other hand, the reaction of 4-nitro-3-(trimethylsilylethynyl)pyridine (**27**) with sodium ethoxide gave resinous products, and neither the corresponding ethyl enolether (**28**) nor the diethyl acetal (**29**) was obtained. Accordingly, it is necessary to devise another method for the construction of the pyrrolo[3,2-*c*]pyridine nucleus.

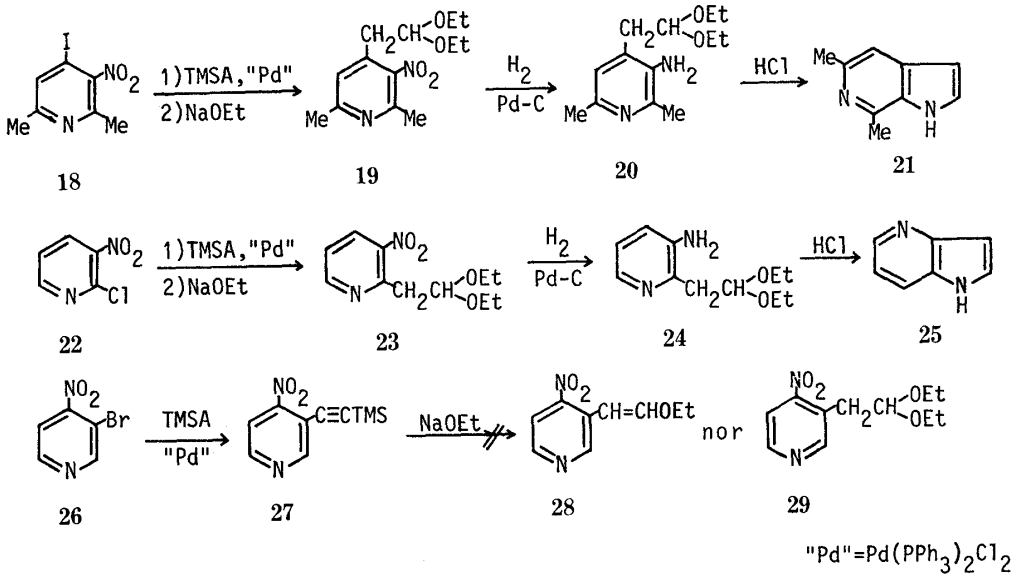
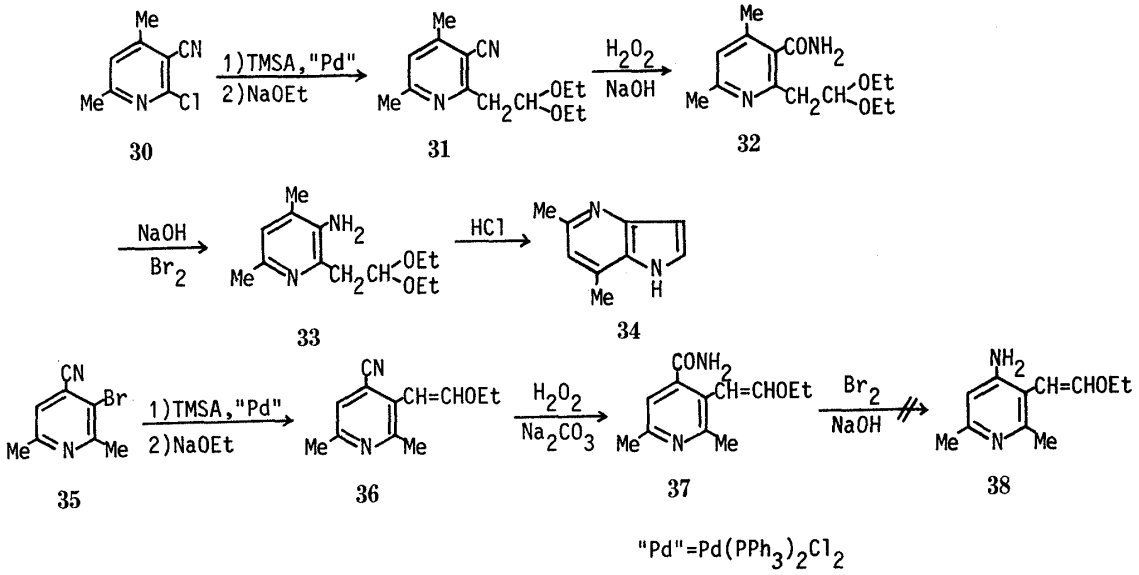


Chart 4

Thus, Hofmann rearrangement of a primary carbamoyl group was investigated in place of hydrogenation of the nitro group for the introduction of an amino group into the pyridine nucleus. As illustrated in Chart 5, this approach was successful at the 3-position of the pyridine derivative. Namely, 2-(2,2-diethoxyethyl)-4,6-dimethyl-3-pyridinecarboxamide (**32**), prepared through the route shown in Chart 5, was readily converted to the 3-aminopyridine (**33**) in good yield under usual conditions of Hofmann rearrangement. Treatment of the aldehyde acetal (**33**) with hydrochloric acid gave 5,7-dimethylpyrrolo[3,2-*b*]pyridine (**34**). However, the introduction of an amino group at the 4-position of the pyridine nucleus by this method was unsuccessful. Namely, the Hofmann rearrangement of the pyridinecarboxamide (**37**) resulted in the formation of resinous material, although every step in the synthesis of **37** from 3-bromo-2,6-dimethyl-4-pyridinecarbonitrile (**35**) proceeded smoothly to give the desired product.

The essence of our condensed pyrrole formation is cyclodehydration between a formylmethyl group, derived from an ethynyl group, and an adjacent amino group. At present, the formation of a formylmethyl group relies on the cross-coupling reaction of *o*-halonitroaromatics with TMSA, but further investigation is necessary for the synthesis of pyrrolo[3,2-*c*]- and pyrrolo[2,3-*b*]pyridine derivatives.



30 31 32 33 34 35 36 37 38

Chart 5

Experimental

All melting points and boiling points are uncorrected. Infrared (IR) spectra were measured with a JASCO IRA-1 spectrometer. Proton nuclear magnetic resonance (^{1}H-NMR) spectra were taken at 60 MHz with a JEOL JNM-PMX 60 spectrometer, and chemical shifts are expressed in δ (ppm) values relative to Me_4Si as an internal standard. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, and br=broad.

2-(2,2-Diethoxyethyl)nitrobenzene (5)——A mixture of 2-bromonitrobenzene (**4a**) (2.02 g, 10 mmol), TMSA (1.5 g, 15 mmol), $Pd(PPh_3)_2Cl_2$ (160 mg), CuI (80 mg), and Et_3N (15 ml) was stirred at room temperature for 14 h. After removal of the Et_3N by evaporation, the residue was diluted with H_2O and extracted with ether. After removal of the ether, the crude product was added to an EtONa–EtOH solution [prepared from dry EtOH (60 ml) and Na (1.15 g, 50 mmol)], and the mixture was refluxed for 4 h. After removal of the EtOH, the residue was diluted with H_2O and extracted with $CHCl_3$. The $CHCl_3$ extract was distilled under reduced pressure to give a pale yellow liquid, bp 120—125 °C (5 mmHg). Yield 930 mg (39%). IR (neat) cm^{-1}: 1550, 1360. ^{1}H-NMR ($CDCl_3$): 1.15 (6H, t, J=7.0 Hz), 3.12 (2H, d, J=6.0 Hz), 3.4—3.9 (4H, m), 4.50 (1H, t, J=6.0 Hz), 7.2—7.6 (3H, m), 7.7—8.0 (1H, m). *Anal.* Calcd for $C_{12}H_{17}NO_4$: C, 60.24; H, 7.16; N, 5.85. Found: C, 60.26; H, 7.19; N, 5.67.

2-(2,2-Diethoxyethyl)aniline (6)——A solution of **5** (700 mg, 2.9 mmol) in EtOH (20 ml) was hydrogenated over 5% Pd–C (300 mg) under atmospheric pressure at room temperature. After H_2 absorption had ceased, the catalyst was removed by filtration. The filtrate was concentrated to dryness, and the residue was distilled under reduced pressure to give a colorless liquid, bp 90—95 °C (4 mmHg). Yield 600 mg (98%). IR ($CHCl_3$) cm^{-1}: 3650, 3370. ^{1}H-NMR ($CDCl_3$): 1.10 (6H, t, J=7.0 Hz), 3.10 (2H, d, J=6.0 Hz), 3.3—3.7 (4H, m), 4.10 (2H, br s), 4.46 (1H, t, J=6.0 Hz), 7.1—7.4 (3H, m), 7.5—7.7 (1H, m). *Anal.* Calcd for $C_{12}H_{19}NO_2$: C, 68.86; H, 9.15; N, 6.69. Found: C, 68.90; H, 9.23; N, 6.47.

Indole (7a)——A solution of **6** (500 mg, 2.4 mmol) and conc. HCl (1 ml) in EtOH (20 ml) was refluxed for 1 h. After removal of the EtOH, the residue was diluted with H_2O, made alkaline with Na_2CO_3, and extracted with $CHCl_3$. The crude product obtained from the $CHCl_3$ extract was recrystallized from hexane to give colorless scales, mp 50—51 °C (lit.[5] mp 51—52 °C). Yield 250 mg (89%). IR ($CHCl_3$) cm^{-1}: 3440. ^{1}H-NMR ($CDCl_3$): 6.4—6.7 (1H, m), 7.0—7.5 (4H, m), 7.5—7.8 (1H, m), 8.0 (1H, br s).

2-(2-Ethoxyethenyl)-3-methylnitrobenzene (8)——A mixture of 2-bromo-3-methylnitrobenzene[6] (**4b**) (2.16 g, 10 mmol), TMSA (1.5 g, 15 mmol), $Pd(PPh_3)_2Cl_2$ (200 mg), CuI (100 mg), and Et_3N (20 ml) was refluxed for 24 h. After removal of the Et_3N, the residue was diluted with H_2O and extracted with ether. The ethereal extract was purified by SiO_2 column chromatography using hexane as an eluent. The crude product obtained from the hexane eluate was added to an EtONa–EtOH solution [prepared from dry EtOH (60 ml) and Na (1.15 g, 50 mmol)], and the mixture was refluxed for 6 h. After removal of the EtOH, the residue was diluted with H_2O and extracted with $CHCl_3$. The $CHCl_3$ extract was purified by SiO_2 column chromatography using hexane–C_6H_6 (9 : 1) as an eluent. The crude product obtained from the hexane–C_6H_6 (9 : 1) eluate was distilled under reduced pressure to afford a pale yellow liquid, bp 130—135 °C (16 mmHg). Yield 1.72 g (83%). IR (neat) cm^{-1}: 1560, 1360. ^{1}H-NMR ($CDCl_3$): 1.20 (3H, t, J=7.0 Hz), 2.25 (3H, s), 3.85 (2H, q, J=7.0 Hz), 5.40 (1H, d, J=7.0 Hz), 6.20 (1H, d, J=7.0 Hz), 7.1—7.7 (3H, m). *Anal.* Calcd for $C_{11}H_{13}NO_3$: C, 63.75; H, 6.31; N, 6.76. Found: C, 63.90; H, 6.29; N, 6.63.

2-Methyl-6-nitrophenylacetaldehyde Ethylene Acetal (9)——A mixture of **8** (1.03 g, 5 mmol), conc. HCl (1 ml), and ethylene glycol (10 ml) was heated at 60 °C for 20 h. The mixture was poured onto ice, made alkaline with K_2CO_3, and extracted with C_6H_6. The C_6H_6 extract was washed with H_2O, and purified by SiO_2 column chromatography using C_6H_6 as an eluent. The crude product obtained from the C_6H_6 eluate was distilled under reduced pressure to give a pale yellow liquid, bp 120—125 °C (5 mmHg). Yield 950 mg (85%). IR (neat) cm^{-1}: 1550, 1350. ^{1}H-NMR ($CDCl_3$): 2.46 (3H, s), 3.36 (2H, d, J=4.0 Hz), 3.70 (4H, s), 5.03 (1H, t, J=4.0 Hz), 7.0—7.7 (3H, m). *Anal.* Calcd for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87; N, 6.28. Found: C, 58.95; H, 5.73; N, 6.16.

2-Amino-6-methylphenylacetaldehyde Ethylene Acetal (10)——A solution of **9** (600 mg, 2.7 mmol) in MeOH (20 ml) was hydrogenated over 5% Pd–C (300 mg) under atmospheric pressure at room temperature. After H_2 absorption had ceased, the catalyst was removed by filtration. The filtrate was concentrated to dryness under reduced pressure, and the residue was recrystallized from cyclohexane to give colorless needles, mp 145—147 °C. Yield 470 mg (90%). IR ($CHCl_3$) cm^{-1}: 3640, 3380. ^{1}H-NMR ($CDCl_3$): 2.35 (3H, s), 3.40 (2H, d, J=4.0 Hz), 3.85 (4H, s), 5.15 (1H, t, J=4.0 Hz), 5.50 (2H, br s), 7.0—7.4 (2H, m), 7.5—7.9 (1H, m). *Anal.* Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.40; H, 7.65; N, 7.12.

4-Methylindole (7b)——A solution of **10** (400 mg, 2.1 mmol) and conc. HCl (1 ml) in EtOH (20 ml) was refluxed for 0.5 h. After removal of the EtOH, the residue was diluted with H_2O, made alkaline with Na_2CO_3, and extracted with $CHCl_3$. The crude product obtained from the $CHCl_3$ extract was distilled under reduced pressure to give a colorless liquid, bp 110—115 °C (5 mmHg) (lit.[7] bp 256 °C). Yield 130 mg (47%). IR ($CHCl_3$) cm^{-1}: 3450. ^{1}H-NMR ($CDCl_3$): 2.55 (3H, s), 6.5—6.7 (1H, m), 6.8—7.6 (4H, m), 8.10 (1H, br s).

3-Ethoxy-5-nitro-3,4-dihydroisocoumarin (13)——A mixture of ethyl 2-bromo-3-nitrobenzoate (**11**)[8] (2.75 g, 10 mmol), TMSA (1.2 g, 12 mmol), $Pd(PPh_3)_2Cl_2$ (200 mg), CuI (100 mg), and Et_3N (20 ml) was refluxed for 12 h. After removal of the Et_3N, the residue was diluted with H_2O and extracted with ether. The ethereal extract was purified by SiO_2 column chromatography using hexane–C_6H_6 (9 : 1) as an eluent. The crude product obtained from the hexane–C_6H_6 (9 : 1) eluate was added to an EtONa–EtOH solution [prepared from dry EtOH (50 ml) and Na (1.15 g, 50 mmol)], and the mixture was refluxed for 1 h. After removal of the EtOH, the residue was diluted with H_2O, acidified with 3 N HCl, and extracted with $CHCl_3$. The product obtained from the $CHCl_3$ extract was recrystallized from hexane–ether to give pale yellow prisms, mp 94—95 °C. Yield 1.1 g (47%). IR ($CHCl_3$) cm^{-1}: 1740, 1540, 1360. ^{1}H-NMR ($CDCl_3$): 1.20 (3H, t, J=7.0 Hz), 2.9—3.1 (2H, m), 3.5—4.3 (2H, m), 5.50 (1H, t, J=4.0 Hz), 6.8—7.7 (3H, m), *Anal.* Calcd for $C_{11}H_{11}NO_5$: C, 55.69; H, 4.67; N, 5.91. Found: C, 55.58; H, 4.72; N, 5.76.

5-Amino-3-ethoxy-3,4-dihydroisocoumarin (16)——A solution of **13** (500 mg, 2.1 mmol) in EtOH (20 ml) was hydrogenated over 5% Pd–C (200 mg) under atmospheric pressure at room temperature. After H_2 absorption had ceased, the catalyst was removed by filtration. The filtrate was concentrated to dryness under reduced pressure, and the residue was recrystallized from hexane to give colorless needles, mp 143—144 °C. Yield 430 mg (85%). IR ($CHCl_3$) cm^{-1}: 3660, 3360, 1740. ^{1}H-NMR ($CDCl_3$): 1.20 (3H, t, J=6.0 Hz), 2.9—3.1 (2H, m), 3.3—4.3 (4H, m), 5.60 (1H, t, J=4.0 Hz), 6.9—7.8 (3H, m). *Anal.* Calcd for $C_{11}H_{13}NO_3$: C, 63.75; H, 6.32; N, 6.76. Found: C, 63.51; H, 6.35; N, 6.83.

Ethyl 4-Indolecarboxylate (17)——Compound **16** (207 mg, 1 mmol) was added to an EtONa–EtOH solution prepared from dry EtOH (20 ml) and Na (46 mg, 2 mmol), and the mixture was stirred at room temperature for 1 h. After removal of the EtOH, the residue was diluted with H_2O and extracted with $CHCl_3$. The crude product obtained from the $CHCl_3$ extract was recrystallized from hexane to give colorless needles, mp 72—73 °C (lit.[9] mp 71—72 °C). Yield 142 mg (75%). IR ($CHCl_3$) cm^{-1}: 3470, 1720. ^{1}H-NMR ($CDCl_3$): 1.45 (3H, t, J=7.0 Hz), 4.43 (2H, q, J=7.0 Hz), 7.0—8.1 (5H, m), 8.2—8.8 (1H, br s).

4-(2,2-Diethoxyethyl)-2,6-dimethyl-3-nitropyridine (19)——A mixture of 4-iodo-2,6-dimethyl-3-nitropyridine (**18**)[10] (5.56 g, 20 mmol), TMSA (2.5 g, 25 mmol), $Pd(PPh_3)_2Cl_2$ (200 mg), CuI (100 mg), and Et_3N (20 ml) was stirred at room temperature for 24 h. After removal of the Et_3N, the residue was diluted with H_2O and extracted with $CHCl_3$. The $CHCl_3$ extract was purified by SiO_2 column chromatography using C_6H_6 as an eluent. The crude product obtained from the C_6H_6 eluate was added to an EtONa–EtOH solution [prepared from dry EtOH (100 ml) and Na (2.3 g, 0.1 mol)], and the mixture was refluxed for 12 h. After removal of the EtOH, the residue was diluted with H_2O and extracted with $CHCl_3$. The $CHCl_3$ extract was distilled under reduced pressure to give a pale yellow liquid, bp 105—107 °C (2 mmHg). Yield 2.2 g (41%). IR (neat) cm^{-1}: 1560, 1340. ^{1}H-NMR (CCl_4): 1.13 (6H, t, J=7.0 Hz), 2.50 (6H, s), 2.80 (2H, d, J=5.0 Hz), 3.2—3.8 (4H, m), 4.50 (1H, t, J=5.0 Hz), 7.00 (1H, s). *Anal.* Calcd for $C_{13}H_{20}N_2O_4$: C, 58.19; H, 7.51; N, 10.44. Found: C, 57.91; H, 7.30; N, 10.20.

3-Amino-4-(2,2-diethoxyethyl)-2,6-dimethylpyridine (20)——A solution of **19** (1.34 g, 5 mmol) in EtOH (15 ml) was hydrogenated over 5% Pd–C (500 mg) under atmospheric pressure at room temperature. After H_2 absorption had ceased, the catalyst was removed by filtration. The filtrate was distilled under reduced pressure to give a pale yellow liquid, bp 130—135 °C (4 mmHg). Yield 840 mg (71%). IR ($CHCl_3$) cm^{-1}: 3650, 3350. ^{1}H-NMR ($CDCl_3$): 1.15 (6H, t, J=7.0 Hz), 2.40 (6H, s), 2.86 (2H, d, J=5.0 Hz), 3.3—4.1 (6H, m), 4.60 (1H, t, J=5.0 Hz), 6.70 (1H, s). *Anal.* Calcd for $C_{13}H_{22}N_2O_2$: C, 65.51; H, 9.31; N, 11.76. Found: C, 65.65; H, 9.16; N, 11.79.

5,7-Dimethylpyrrolo[2,3-*c*]pyridine (21)——A solution of **20** (500 mg, 2.1 mmol) and conc. HCl (2 ml) in EtOH

(20 ml) was refluxed for 1 h. After removal of the EtOH, the residue was diluted with H_2O, made alkaline with K_2CO_3, and extracted with $CHCl_3$. The crude product obtained from the $CHCl_3$ extract was recrystallized from cyclohexane to give colorless prisms, mp 138—139 °C. Yield 210 mg (68%). IR ($CHCl_3$) cm^{-1}: 3470. ^{1}H-NMR ($CDCl_3$): 2.51 (3H, s), 2.66 (3H, s), 6.47 (1H, d, J=3.0 Hz), 7.2—7.4 (2H, m), 9.30 (1H, br s). *Anal.* Calcd for $C_9H_{10}N_2$: C, 73.94; H, 6.90; N, 19.16. Found: C, 73.72; H, 6.65; N, 19.03.

2-(2,2-Diethoxyethyl)-3-nitropyridine (23)——A mixture of 2-chloro-3-nitropyridine (**22**)[11] (1.58 g, 10 mmol), TMSA (1.5 g, 15 mmol), $Pd(PPh_3)_2Cl_2$ (160 mg), CuI (80 mg), and Et_3N (3 ml) was heated in a sealed tube at 100 °C for 5 h. The mixture was diluted with H_2O and extracted with ether. After removal of the ether, the residue obtained from the ethereal extract was added to an EtONa–EtOH solution [prepared from dry EtOH (60 ml) and Na (1.15 g, 50 mmol)], and the mixture was refluxed for 3 h. After removal of the EtOH, the residue was diluted with H_2O and extracted with $CHCl_3$. The $CHCl_3$ extract was distilled under reduced pressure to give a pale yellow liquid, bp 125—130 °C (16 mmHg). Yield 770 mg (32%). IR (neat) cm^{-1}: 1540, 1350. ^{1}H-NMR ($CDCl_3$): 1.20 (6H, t, J=7.0 Hz), 3.05 (2H, d, J=6.0 Hz), 3.3—3.9 (4H, m), 4.60 (1H, t, J=6.0 Hz), 6.9—7.1 (2H, m), 8.0—8.2 (1H, m). *Anal.* Calcd for $C_{11}H_{16}N_2O_4$: C, 54.99; H, 6.71; N, 11.66. Found: C, 54.86; H, 6.55; N, 11.53.

3-Amino-2-(2,2-diethoxyethyl)pyridine (24)——A solution of **23** (600 mg, 2.5 mmol) in EtOH (20 ml) was hydrogenated over 5% Pd–C (300 mg) under atmospheric pressure at room temperature. After H_2 absorption had ceased, the catalyst was removed by filtration. The filtrate was distilled under reduced pressure to give a pale yellow liquid, bp 120—125 °C (4 mmHg). Yield 420 mg (80%). IR ($CHCl_3$) cm^{-1}: 3660, 3360. ^{1}H-NMR ($CDCl_3$): 1.15 (6H, t, J=7.0 Hz), 3.10 (2H, d, J=6.0 Hz), 3.3—4.3 (6H, m), 4.80 (1H, t, J=6.0 Hz), 6.9—7.0 (2H, m), 7.9—8.1 (1H, m). *Anal.* Calcd for $C_{11}H_{18}N_2O_2$: C, 62.83; H, 8.63; N, 13.32. Found: C, 62.71; H, 8.56; N, 13.26.

Pyrrolo[3,2-*b*]pyridine (25)——A solution of **24** (300 mg, 1.4 mmol) and conc. HCl (0.3 ml) in EtOH (10 ml) was refluxed for 1 h. After removal of the EtOH, the residue was diluted with H_2O, made alkaline with Na_2CO_3, and extracted with $CHCl_3$. The crude product obtained from the $CHCl_3$ extract was recrystallized from cyclohexane–acetone to give colorless needles, mp 126—127 °C (lit.[12] mp 127—128 °C). Yield 94 mg (56%). IR ($CHCl_3$) cm^{-1}: 3480. ^{1}H-NMR ($CDCl_3$): 6.5—6.9 (1H, m), 7.0—7.3 (1H, m), 7.4—7.9 (2H, m), 8.4—8.6 (1H, m), 10.85 (1H, br s).

2-(2,2-Diethoxyethyl)-4,6-dimethyl-3-pyridinecarbonitrile (31)——A mixture of 2-chloro-4,6-dimethyl-3-pyridinecarbonitrile (**30**)[13] (3.33 g, 20 mmol), TMSA (2.4 g, 24 mmol), $Pd(PPh_3)_2Cl_2$ (300 mg), CuI (150 mg), and Et_3N (4 ml) was heated in a sealed tube at 120 °C for 6 h. The mixture was diluted with H_2O and extracted with ether. The ethereal extract was purified by SiO_2 column chromatography using $CHCl_3$ as an eluent. The product obtained from the $CHCl_3$ eluate, was added to an EtONa–EtOH solution [prepared from dry EtOH (100 ml) and Na (2.3 g, 100 mmol)], and the mixture was refluxed for 6 h. After removal of the EtOH, the residue was diluted with H_2O and extracted with $CHCl_3$. The $CHCl_3$ extract was distilled under reduced pressure to give a pale yellow liquid, bp 120—125 °C (4 mmHg). Yield 3.32 g (67%). IR ($CHCl_3$) cm^{-1}: 2210. ^{1}H-NMR ($CDCl_3$): 1.10 (6H, t, J=7.0 Hz), 2.50 (6H, s), 3.20 (2H, d, J=6.0 Hz), 3.3—3.9 (4H, m), 4.95 (1H, t, J=6.0 Hz), 6.90 (1H, s). *Anal.* Calcd for $C_{14}H_{20}N_2O_2$: C, 67.71; H, 8.12; N, 11.27. Found: C, 67.62; H, 8.07; N, 11.21.

2-(2,2-Diethoxyethyl)-4,6-dimethyl-3-pyridinecarboxamide (32)——A mixture of **31** (1.24 g, 5 mmol), 3 N NaOH (30 ml), 30% H_2O_2 (10 ml), and MeOH (20 ml) was stirred at room temperature for 24 h. After concentration of the mixture under reduced pressure, the residue was diluted with H_2O and extracted with $CHCl_3$. The crude product obtained from the $CHCl_3$ extract was recrystallized from cyclohexane to give colorless scales, mp 115—116 °C. Yield 1.1 g (83%). IR ($CHCl_3$) cm^{-1}: 3500, 3380, 1680. ^{1}H-NMR ($CDCl_3$): 1.05 (6H, t, J=7.0 Hz), 2.46 (6H, s), 3.15 (2H, d, J=6.0 Hz), 3.2—3.7 (4H, m), 4.80 (1H, t, J=6.0 Hz), 6.40 (2H, br s), 6.85 (1H, s). *Anal.* Calcd for $C_{14}H_{22}N_2O_3$: C, 63.13; H, 8.32; N, 10.52. Found: C, 63.01; H, 8.32; N, 10.56.

3-Amino-2-(2,2-diethoxyethyl)-4,6-dimethylpyridine (33)——Compound **32** (1.0 g, 3.7 mmol) was added to an NaOBr solution [prepared from Br_2 (3.2 g, 20 mmol), NaOH (2.4 g, 60 mmol), and H_2O (30 ml)] at 0 °C. The mixture was stirred at 0 °C for 1 h and then heated at 80 °C for 1 h. After cooling, the mixture was extracted with $CHCl_3$. The crude product obtained from the $CHCl_3$ extract was distilled under reduced pressure to give a colorless liquid, bp 140—150 °C (2 mmHg). Yield 600 mg (67%). IR ($CHCl_3$) cm^{-1}: 3650, 3350. ^{1}H-NMR ($CDCl_3$): 1.16 (6H, t, J=7.0 Hz), 2.10 (3H, s), 2.30 (3H, s), 2.95 (2H, d, J=6.0 Hz), 3.3—3.9 (6H, m), 4.65 (1H, t, J=6.0 Hz), 6.60 (1H, s). *Anal.* Calcd for $C_{13}H_{22}N_2O_2$: C, 65.52; H, 9.31; N, 11.76. Found: C, 65.33; H, 9.16; N, 11.58.

5,7-Dimethylpyrrolo[3,2-*b*]pyridine (34)——A solution of **33** (500 mg, 2.1 mmol) and conc. HCl (2 ml) in EtOH (20 ml) was refluxed for 2 h. After removal of the EtOH, the residue was diluted with H_2O, made alkaline with K_2CO_3, and extracted with $CHCl_3$. The crude product obtained from the $CHCl_3$ extract was recrystallized from C_6H_6 to give colorless needles, mp 177—178 °C. Yield 220 mg (72%). IR ($CHCl_3$) cm^{-1}: 3480. ^{1}H-NMR ($CDCl_3$): 2.45 (3H, s), 2.60 (3H, s), 6.5—6.6 (1H, m), 6.85 (1H, s), 7.3—7.5 (1H, m), 9.65 (1H, br s). *Anal.* Calcd for $C_9H_{10}N_2$: C, 73.94; H, 6.90; N, 19.16. Found: C, 73.72; H, 6.87; N, 19.08.

3-Bromo-2,6-dimethyl-4-pyridinecarbonitrile (35)——A mixture of 3-bromo-2,6-dimethylpyridine 1-oxide[14] (3.03 g, 15 mmol) and dimethyl sulfate (1.89 g, 15 mmol) was heated at 70 °C for 2 h. After cooling of the mixture, a solution of KCN (1.95 g, 30 mmol) in H_2O (20 ml) was added with stirring. The whole was stirred at room temperature for 4 h, then made alkaline with K_2CO_3, and extracted with $CHCl_3$. The $CHCl_3$ extract was purified by

SiO_2 column chromatography using $CHCl_3$ as an eluent. The product obtained from the $CHCl_3$ eluate was recrystallized from hexane to give colorless needles, mp 84—85 °C. Yield 1.50 g (47%). IR ($CHCl_3$) cm^{-1}: 2220. ^1H-NMR ($CDCl_3$): 2.53 (3H, s), 2.70 (3H, s), 7.23 (1H, s). *Anal.* Calcd for $C_8H_7BrN_2$: C, 45.53; H, 3.34; N, 13.27. Found: C, 45.57; H, 3.23; N, 13.14.

3-(2-Ethoxyethenyl)-2,6-dimethyl-4-pyridinecarbonitrile (36)——A mixture of **35** (1.06 g, 5 mmol), TMSA (750 mg, 7.5 mmol), $Pd(PPh_3)_2Cl_2$ (100 mg), CuI (50 mg), and Et_3N (1 ml) was heated in a sealed tube at 80 °C for 7 h. The mixture was diluted with H_2O and extracted with ether. The ethereal extract was purified by SiO_2 column chromatography using C_6H_6 as an eluent. The product obtained from the C_6H_6 eluate was added to an EtONa–EtOH solution [prepared from dry EtOH (20 ml) and Na (230 mg, 10 mmol)], and the mixture was heated at 50 °C for 16 h. After removal of the EtOH, the residue was diluted with H_2O and extracted with $CHCl_3$. The crude product obtained from the $CHCl_3$ extract, was distilled under reduced pressure to give a colorless liquid, bp 130—135 °C (2 mmHg). Yield 600 mg (59%). IR ($CHCl_3$) cm^{-1}: 2220. ^1H-NMR ($CDCl_3$): 1.30 (3H, t, $J=7.0$ Hz), 2.55 (6H, s), 4.00 (2H, q, $J=7.0$ Hz), 5.30 (1H, d, $J=7.0$ Hz), 6.45 (1H, d, $J=7.0$ Hz), 7.20 (1H, s). *Anal.* Calcd for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 70.97; H, 6.65; N, 13.72.

3-(2-Ethoxyethenyl)-2,6-dimethyl-4-pyridinecarboxamide (37)——A mixture of **36** (500 mg, 2.5 mmol), 3 N Na_2CO_3 (10 ml), 30% H_2O_2 (5 ml), and MeOH (5 ml) was stirred at room temperature for 24 h. After concentration of the mixture, the residue was diluted with H_2O and extracted with $CHCl_3$. The $CHCl_3$ extract was recrystallized from cyclohexane to give colorless needles, mp 165—167 °C. Yield 450 mg (83%). IR ($CHCl_3$) cm^{-1}: 3500. 3390, 1680. ^1H-NMR ($CDCl_3$): 1.25 (3H, t, $J=7.0$ Hz), 2.50 (6H, s), 3.90 (2H, q, $J=7.0$ Hz), 5.35 (1H, d, $J=7.0$ Hz), 6.30 (3H, m), 7.16 (1H, s). *Anal.* Calcd for $C_{12}H_{16}NO_2$: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.31; H, 7.15; N, 12.53.

References and Notes

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