[Chem. Pharm. Bull. 35(5)1823—1828(1987)]

Condensed Heteroaromatic Ring Systems. XII.[1] Synthesis of Indole Derivatives from Ethyl 2-Bromocarbanilates

TAKAO SAKAMOTO, YOSHINORI KONDO, SHIGEKI IWASHITA, and HIROSHI YAMANAKA*

Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

(Received October 29, 1986)

The palladium-catalyzed reaction of ethyl 2-bromocarbanilate with trimethylsilylacetylene yielded ethyl 2-(trimethylsilylethynyl)carbanilate, which was treated with sodium ethoxide to give indole. The carbanilates having a methyl or a bromo substituent were similarly transformed to corresponding indole derivatives. Furthermore, pyrrolo[3,2-*b*]- and pyrrolo[3,2-*c*]pyridines were synthesized by this method.

Keywords——palladium-catalyzed reaction; trimethylsilylacetylene; ethyl 2-halocarbanilate; ethyl 2-halopyridinecarbamate; ethyl 2-(trimethylsilylethynyl)carbanilate; ethyl *o*-(trimethylsilylethynyl)pyridinecarbamate; indole; pyrrolopyridine

When ethyl 2-nitrophenylpyruvate is hydrogenated in the presence of platinum oxide, the resulting ethyl 2-aminophenylpyruvate undergoes spontaneous dehydro-cyclization to give ethyl 2-indolecarboxylate.[2] The reaction is named as the Reissert indole synthesis. We have previously reported[3] a Reissert-type indole synthesis from 2-(2,2-diethoxyethyl)nitrobenzene, which was obtained by the palladium-catalyzed reaction of 2-bromonitrobenzene and trimethylsilylacetylene (TMSA), followed by the reaction with sodium ethoxide.

On the other hand, there are some reports of the cyclization of 2-ethynylanilines to indoles in the presence of cuprous halides through intramolecular addition of the amino group to the ethynyl group.[4] We describe in this paper another synthetic method to obtain indoles from 2-ethynylaniline derivatives, which were prepared from 2-haloacylanilines by the palladium-catalyzed reaction with TMSA.

The reaction of 2-bromoaniline itself (**1**) with TMSA in the presence of dichlorobis(triphenylphosphine)palladium and cuprous iodide in triethylamine[5] resulted in the recovery of **1**, whereas 2-bromoacetanilide (**2b**) reacted with TMSA under the same conditions to give 2-(trimethylsilylethynyl)acetanilide (**3b**) in moderate yield. When **3b** was heated with sodium ethoxide in ethanol under reflux, indole (**4**) was obtained in 34% yield with a concomitant formation of 2-ethynylaniline (**5**) in 39% yield.

Based on the above results, several acyl derivatives of **1** were examined in order to estimate the efficiency of protecting groups for the cross-coupling reaction with TMSA and the indole cyclization. As a result, ethyl 2-bromocarbanilate (**2e**) was ascertained to be the most satisfactory substrate for both reactions. That is, the carbanilate (**2e**) smoothly reacted with TMSA to give ethyl 2-(trimethylsilylethynyl)carbanilate (**3e**), which was convertible to indole (**4**) by treatment with sodium ethoxide in almost quantitative yield.

Additionally, 2-ethynylaniline (**5**) was heated with sodium ethoxide in ethanol under reflux for 24 h, but no indole formation was observed, and **5** was recovered. Accordingly, it is likely that **3a**—**e** were changed to indole (**4**) by way of the 1-acylindoles (**6**).

According to the procedure described above, all the indole derivatives (**10a**—**d**)

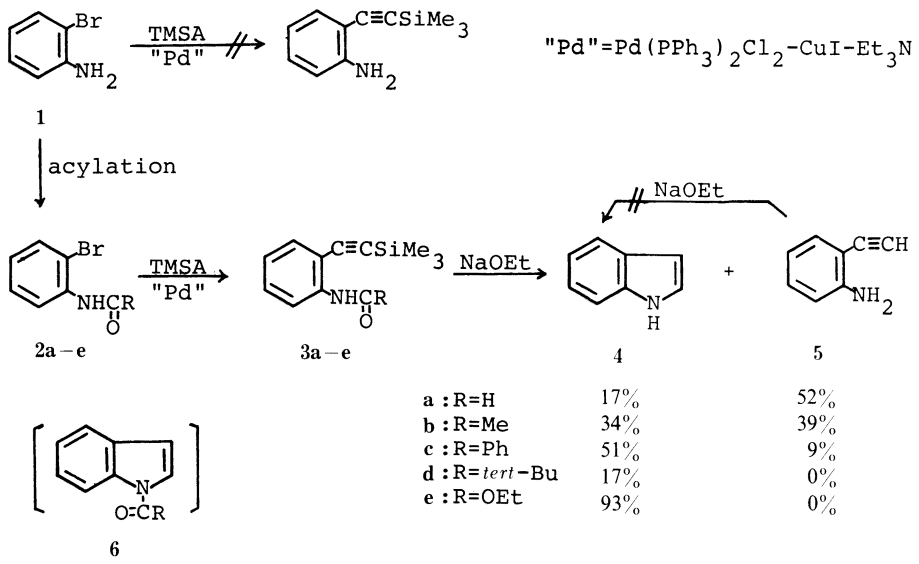


Chart 1

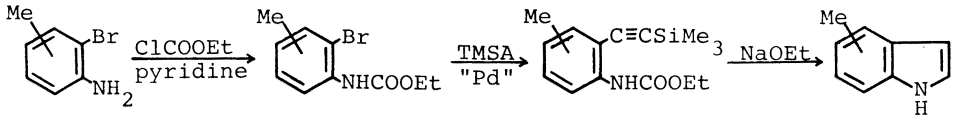
TABLE I. 2-(Trimethylsilylethynyl)acetylenes (**3a—e**)

No.	Yield (%)	mp (°C) [bp/mmHg]	IR ($CHCl_3$) cm^{-1}	^{1}H-NMR ($CDCl_3$) δ (ppm)
3a	45	78—80	2120 1700	0.30 (9H, s), 7.0—7.6 (3H, m), 7.90 (1H, br s), 8.3—8.6 (2H, m)
3b	61	96—97	2120 1685	0.30 (9H, s), 2.17 (3H, s), 6.9—7.6 (3H, m), 8.00 (1H, br s), 8.2—8.5 (1H, m)
3c	50	84—85.5	2120 1680	0.30 (9H, s), 6.9—7.7 (6H, m), 7.8—8.1 (2H, m), 8.5—8.8 (1H, m), 8.95 (1H, br s)
3d	51	[130—135/3]	2120 1680	0.29 (9H, s), 1.90 (9H, s), 6.8—7.5 (3H, m), 8.25 (1H, br s), 8.3—8.6 (1H, m)
3e	86	[133/4]	2120 1725	0.30 (9H, s), 1.30 (3H, t, J=7.0 Hz), 4.20 (2H, q, J=7.0 Hz), 6.8—7.5 (4H, m), 8.1—8.3 (1H, m)

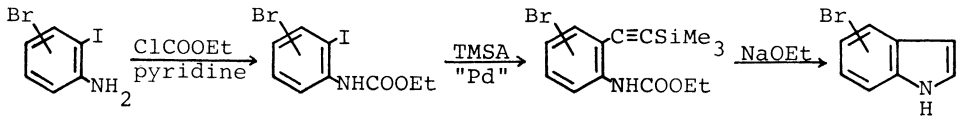
containing a methyl group on the fused benzene ring were easily synthesized from the corresponding bromotoluidines (**7a—d**) *via* the carbanilates (**8a—d**). For example, 2-bromo-5-methylaniline (**7c**) was converted to ethyl 2-bromo-5-methylcarbanilate (**8c**) by treatment with ethyl chloroformate in pyridine. When ethyl 5-methyl-2-(trimethylsilylethnyl)carbanilate (**9c**), obtained from the reaction of **8c** with TMSA, was treated with sodium ethoxide, 6-methylindole (**10c**) was obtained; this is a simple and practical reaction. Further results are listed in Table II.

It is known that in the palladium-catalyzed cross-coupling reaction with terminal acetylenes, aryl iodides commonly show higher reactivity than aryl bromides. Thus, the synthesis of 5-bromo- (**14a**) and 6-bromoindole (**14b**) was achieved by the cross-coupling reaction of ethyl 4-bromo-2-iodocarbanilate (**12a**) and 5-bromo-2-iodocarbanilate (**12b**) with TMSA, followed by treatment with sodium ethoxide.

The above method was successfully applied to the synthesis of pyrrolo[3,2-*b*]pyridine (**18**) and pyrrolo[3,2-*c*]pyridine (**25**), as shown in Chart 3. As reported previously, **18** can be synthesized from 2-bromo-3-nitropyridine (**19**) by using the cross-coupling reaction with



7a : 3-Me **8a** : 3-Me **9a** : 3-Me **10a** : 4-Me
7b : 4-Me **8b** : 4-Me **9b** : 4-Me **10b** : 5-Me
7c : 5-Me **8c** : 5-Me **9c** : 5-Me **10c** : 6-Me
7d : 6-Me **8d** : 6-Me **9d** : 6-Me **10d** : 7-Me

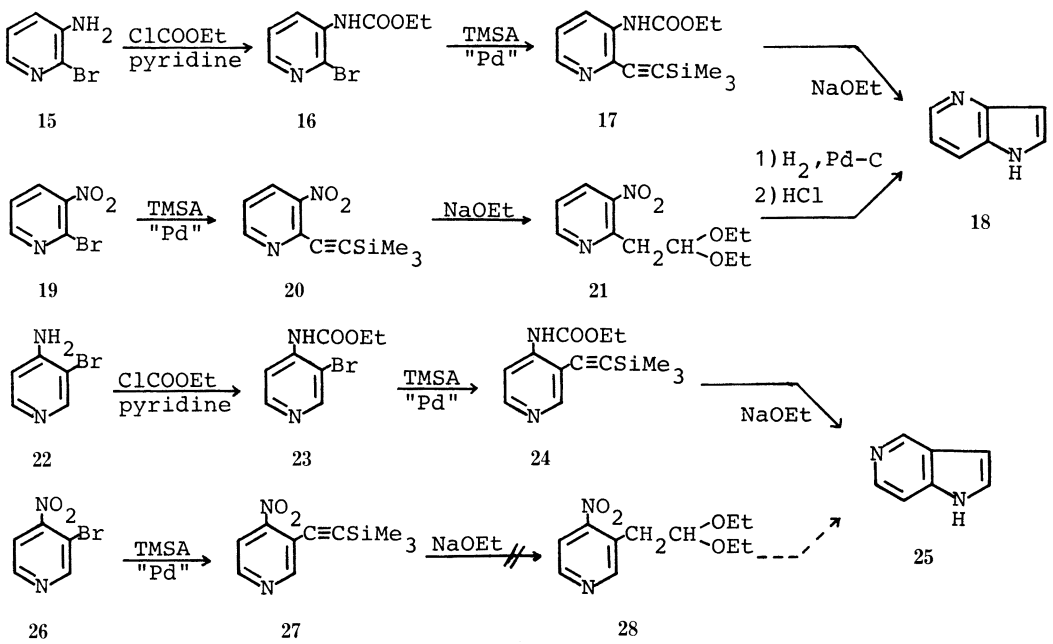


11a : 4-Br **12a** : 4-Br **13a** : 4-Br **14a** : 5-Br
11b : 5-Br **12b** : 5-Br **13b** : 5-Br **14b** : 6-Br

Chart 2

TABLE II. Methyl- (**10a—d**) and Bromoindoles (**14a, b**)

No.	Yield (%)	bp/mmHg [mp] (°C)	Lit. bp/mmHg [mp] (°C)	IR ($CHCl_3$) cm^{-1}	^{1}H-NMR (CCl_4) δ (ppm)
10a	18	120—130/20	90/15[6]	3440	2.50 (3H, s), 6.3—6.5 (1H, m), 6.6—7.1 (4H, m), 7.70 (1H, brs)
10b	78	100—105/3	267[7]	3490	2.41 (3H, s), 5.9—7.6 (6H, m)
10c	47	100—103/3	112/5[8]	3490	2.40 (3H, s), 6.0—7.6 (6H, m)
10d	59	110—115/3	226[7]	3490	2.45 (3H, s), 6.4—7.7 (5H, m), 7.93 (1H, brs)
14a	46	[87—89]	[85.5—86][9]	3480	6.4—6.6 (1H, m), 7.1—7.4 (3H, m), 7.80 (2H, s)
14b	34	[93.5—94]	[93.5—94][10]	3480	6.3—6.5 (1H, m), 6.9—7.5 (4H, m), 7.82 (1H, brs)



15 **16** **17** **18**

19 **20** **21**

22 **23** **24** **25**

26 **27** **28**

Chart 3

TMSA as a key reaction. The same compound (**18**) was obtained alternatively from **15**, which is more readily available than **19**. An attempted synthesis of **25** from 3-bromo-4-nitropyridine (**26**) failed, because the reaction of 3-(trimethylsilylethynyl)-4-nitropyridine (**27**) with sodium ethoxide gave resinous products instead of the desired compound (**28**). However, **25** was successfully prepared from 4-amino-3-bromopyridine (**22**).

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 JMN-PMX 60 spectrometer. Chemical shifts are expressed in δ (ppm) values. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and br = broad.

The following starting materials were prepared by the reported procedures: 2-bromo-3-methyl-,[11] 2-bromo-4-methyl-,[12] 2-bromo-5-methyl-,[13] 2-bromo-6-methyl-,[14] and 4-bromo-2-iodoaniline.[15]

General Procedure for the Preparation of 2-(Trimethylsilylethynyl)-*N*-acylanilines (3a—e)——A mixture of a 2-bromo-*N*-acylaniline (5 mmol), TMSA (7.5 mmol), $Pd(PPh_3)_2Cl_2$ (160 mg), CuI (80 mg), and Et_3N (2 ml) was heated in a sealed tube at 100 °C for 5 h. The reaction mixture was diluted with H_2O and extracted with ether. The ethereal extract was purified by SiO_2 column chromatography using C_6H_6 for **3a**, **b**, **d**, hexane–acetone (20 : 1) for **3c**, or hexane–C_6H_6 (3 : 1) for **3e** as an eluent. The crude product was purified by recrystallization or by distillation under reduced pressure.

Reaction of 3a—e with Sodium Ethoxide——A mixture of **3** (2 mmol) and ethanolic sodium ethoxide [prepared from Na (10 mmol) and dry EtOH (20 ml)] was refluxed until **3** was no longer detectable by SiO_2 thin-layer chromatography. 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 C_6H_6 as an eluent.

5-Bromo-2-iodonitrobenzene——4-Bromoacetanilide (10 g, 47 mmol) was gradually added to fum. HNO_3 (20 ml) below 0 °C. After being stirred for 8 min below 0 °C and for 8 min at room temperature, the mixture was poured into ice-water. A suspension of the resulting precipitate in 3 N KOH (70 ml) was refluxed for 24 h, neutralized with 3 N HCl, and extracted with CH_2Cl_2. Sodium nitrite (1.5 g, 22 mmol) was added to a suspension of the crude product obtained from the CH_2Cl_2 extract in 5 N HCl (12 ml) at 0—10 °C, then an aqueous solution (10 ml) of KI (4.1 g, 25 mmol) was added as a batch. The reaction mixture was stirred at room temperature for 30 min, then heated on a water-bath for 45 min, and made alkaline with K_2CO_3. The resulting precipitate was filtered off and purified by SiO_2 column chromatography using hexane as an eluent. The product, obtained from the hexane eluate, was recrystallized from hexane–ether to give yellow needles, mp 87.5—88 °C. Yield 2.77 g (18%). ^{1}H-NMR ($CDCl_3$): 7.35 (1H, dd, J = 2.0 and 8.0 Hz), 7.86 (1H, d, J = 8.0 Hz), 7.95 (1H, d, J = 2.0 Hz). *Anal.* Calcd for $C_6H_5BrN_2O_2$: C, 21.98; H, 0.92; N, 4.27. Found: C, 22.01; H, 0.85; N, 4.26.

5-Bromo-2-iodoaniline (11b)——A solution of 95% $SnCl_2$ (5.93 g, 30 mmol) in conc. HCl (12 ml) was added to a solution of 5-bromo-2-iodonitrobenzene (2 g, 6.1 mmol) in EtOH (16 ml) at 15—18 °C under stirring. The mixture was heated at 50—60 °C for 15 min, made alkaline with solid KOH, and extracted with $CHCl_3$. The crude product, obtained from the $CHCl_3$ extract, was recrystallized from hexane–ether to give colorless needles, mp 55 °C. Yield 1.25 g (69%). IR ($CHCl_3$) cm^{-1}: 3500, 3390. ^{1}H-NMR (CCl_4): 4.04 (2H, br s), 6.53 (1H, dd, J = 2.0 and 8.0 Hz), 6.75 (1H, d, J = 2.0 Hz), 7.37 (1H, d, J = 8.0 Hz). *Anal.* Calcd for C_6H_5BrIN: C, 24.19; H, 1.69; N, 4.70. Found: C, 23.98; H, 1.65; N, 4.62.

General Procedure for the Preparation of Ethyl 2-Halocarbanilates (8a—d and 12a, b)——Ethyl chloroformate (43 mmol) was added to a solution of a 2-haloaniline (30 mmol) in pyridine (40 ml) at 0—10 °C with stirring, and the

TABLE III. Analytical Data for 2-(Trimethylsilylethynyl)acylanilines (**3a—e**)

No.	Formula	Analysis (%) Calcd C	H	N	Found C	H	N
3a	$C_{12}H_{15}NOSi$	66.31	6.96	6.45	66.06	7.19	6.41
3b	$C_{13}H_{17}NOSi$	67.48	7.41	6.05	67.27	7.62	6.07
3c	$C_{18}H_{19}NOSi$	73.68	6.53	4.77	73.72	6.52	4.86
3d	$C_{16}H_{23}NOSi$	70.28	8.48	5.12	70.12	8.78	5.07
3e	$C_{14}H_{19}NO_2Si$	64.33	7.33	5.36	64.18	7.51	5.05

TABLE IV. Ethyl 2-Halocarbanilates (**8a—d** and **12a, b**)

No.	Yield (%)	bp/mmHg [mp] (°C)	IR ($CHCl_3$) cm^{-1}	^{1}H-NMR (CCl_4) δ (ppm)
8a	99	120/3	3410 1740	1.30 (3H, t, J=7.0 Hz), 2.43 (3H, s), 4.20 (2H, q, J=7.0 Hz), 6.7—7.2 (3H, m), 8.02 (1H, dd, J=2.0 and 8.0 Hz)
8b	89	119—122/4	3420 1735	1.28 (3H, t, J=7.0 Hz), 2.20 (3H, s), 4.16 (2H, q, J=7.0 Hz), 6.7—7.5 (3H, m), 8.04 (1H, d, J=8.0 Hz)
8c	87	115—116/3	3410 1735	1.25 (3H, t, J=7.0 Hz), 2.22 (3H, s), 4.16 (2H, q, J=7.0 Hz), 7.03 (1H, br s), 7.31 (1H, d, J=8.0 Hz), 8.03 (1H, d, J=2.0 Hz)
8d	44	[55—56] (hexane)	3400 1725	1.26 (3H, t, J=7.0 Hz), 2.29 (3H, s), 4.19 (2H, q, J=7.0 Hz), 6.53 (1H, br s), 6.7—7.6 (3H, m)
12a	95	[105—108] (hexane)	3370 1740	1.32 (3H, t, J=7.0 Hz), 4.24 (2H, q, J=7.0 Hz), 6.91 (1H, br s), 7.43 (1H, dd, J=2.0 and 9.0 Hz), 7.88 (1H, d, J=2.0 Hz), 7.98 (1H, d, J=9.0 Hz)
12b	72	[80—81] (hexane)	3385 1735	1.34 (3H, t, J=7.0 Hz), 4.22 (2H, q, J=7.0 Hz), 6.87 (1H, dd, J=2.0 and 8.0 Hz), 7.53 (1H, d, J=8.0 Hz), 8.33 (1H, d, J=2.0 Hz)

TABLE V. Analytical Data for Ethyl 2-Halocarbanilates (**8a—d** and **12a, b**)

No.	Formula	Analysis (%) Calcd C	H	N	Found C	H	N
8a	$C_{10}H_{12}BrNO_2$	46.53	4.70	5.43	46.49	4.61	5.37
8b	$C_{10}H_{12}BrNO_2$	46.53	4.70	5.43	46.61	4.62	5.40
8c	$C_{10}H_{12}BrNO_2$	46.53	4.70	5.43	46.68	4.69	5.31
8d	$C_{10}H_{12}BrNO_2$	46.53	4.70	5.43	46.49	4.91	5.16
12a	$C_9H_9BrINO_2$	29.22	2.45	3.79	29.33	2.45	3.73
12b	$C_9H_9BrINO_2$	29.22	2.45	3.79	29.18	2.34	3.72

mixture was stirred at this temperature for 3 h. After removal of the pyridine, the residue was diluted with H_2O and extracted with ether. The ethereal extract was washed with 3 N HCl and 1 N $NaHCO_3$. The residue, obtained from the ethereal extract was purified by SiO_2 column chromatography, followed by distillation under reduced pressure, or recrystallization.

General Procedure for the Preparation of Methyl- (10a—d) and Bromoindoles (14a, b)——A mixture of **8** or **12** (5 mmol), TMSA (8 mmol), $Pd(PPh_3)_2Cl_2$ (0.25 mmol), CuI (0.4 mmol), and Et_3N (8 mmol) was heated in a sealed tube for 2—3 h at 100—110 °C for **8** or 60 °C for **12**. The mixture was diluted with H_2O and extracted with ether. The ethereal extract was purified by SiO_2 column chromatography. The crude product was added to ethanolic sodium ethoxide (prepared from Na (20 mmol) and dry EtOH (50 ml)), and the mixture was refluxed for 12—24 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, distillation under reduced pressure, or recrystallization.

Ethyl 2-Bromo-3-pyridinecarbamate (16)——According to the general procedure for the preparation of ethyl 2-halocarbanilate, 3-amino-2-bromopyridine (**15**) (10 mmol) was treated with ethyl chloroformate (15 mmol) in pyridine (20 ml) to give colorless needles, mp 52—53 °C, which were recrystallized from hexane. Yield 58%. IR ($CHCl_3$) cm^{-1}: 3390, 1730. ^{1}H-NMR ($CDCl_3$): 1.36 (3H, t, J=7.0 Hz), 4.30 (2H, q, J=7.0 Hz), 7.40 (1H, br s), 8.16 (1H, d, J=6.0 Hz), 8.45 (1H, d, J=6.0 Hz), 8.65 (1H, s). *Anal.* Calcd for $C_8H_9BrN_2O_2$: 39.21; H, 3.70; N, 11.42. Found: C, 39.20; H, 3.59; N, 11.33.

Ethyl 3-Bromo-4-pyridinecarbamate (23)——According to the general procedure for the preparation of ethyl 2-halocarbanilate, 4-amino-3-bromopyridine (10 mmol) was treated with ethyl chloroformate (15 mmol) in pyridine (20 ml) to give colorless needles, mp 60—61.5 °C, which were recrystallized from hexane. Yield 52%. IR ($CHCl_3$) cm^{-1}: 3390, 1730. ^{1}H-NMR ($CDCl_3$): 1.35 (3H, t, J=7.0 Hz), 4.32 (2H, q, J=7.0 Hz), 7.0—7.3 (1H, m), 7.5—7.9 (2H, m), 8.4—8.5 (1H, m). *Anal.* Calcd for $C_8H_9BrN_2O_2$: 39.21; H, 3.70; N, 11.42. Found: C, 39.16; H, 3.63; N, 11.35.

Pyrrolo[3,2-*b*]pyridine (18)——According to the general procedure for the preparation of indoles, treatment of **16** (5 mmol) with TMSA (7.5 mmol) followed by reaction with NaOEt gave colorless needles, mp 126—127 °C, which

were recrystallized from cyclohexane–acetone. Lit.[16] mp 127—128 °C. IR ($CHCl_3$) cm^{-1}: 3480. ^{1}H-NMR ($CDCl_3$): 7.0—7.3 (1H, m), 7.4—7.9 (2H, m), 8.4—8.6 (1H, m), 10.85 (1H, br s).

Pyrrolo[3,2-*c*]pyridine (25)——According to the general procedure for the preparation of indoles, treatment of **23** (5 mmol) with TMSA (7.5 mmol) followed by reaction with NaOEt gave colorless needles, mp 110—111 °C, which were recrystallized from cyclohexane. Lit.[17] mp 111.5—112.5 °C. Yield 58%. IR ($CHCl_3$) cm^{-1}: 3470. ^{1}H-NMR ($CDCl_3$): 6.6—6.9 (1H, m), 7.2—7.4 (2H, m), 8.35 (1H, d, J=5.6 Hz), 9.20 (1H, s), 10.60 (1H, br s).

References and Notes

1) Part X: T. Sakamoto, Y. Kondo, N. Miura, K. Hayashi, and H. Yamanaka, *Heterocycles*, **24**, 2311 (1986). A part of the results in this paper has been published as a communication [T. Sakamoto, Y. Kondo, and H. Yamanaka, *Heterocycles*, **24**, 31 (1986)]
2) W. E. Noland and F. J. Baude, "Organic Syntheses," Coll. Vol. V, ed. by H. E. Baumgarten, John Wiley and Sons, Inc., New York, 1973, p. 567.
3) T. Sakamoto, Y. Kondo, and H. Yamanaka, *Heterocycles*, **22**, 1347 (1984).
4) *a*) S. Horiie, *Nippon Kagaku Zasshi*, **79**, 227 (1958); *b*) J. Reisch, *Chem. Ber.*, **97**, 2717 (1964); *c*) C. E. Castro and R. D. Stephens, *J. Org. Chem.*, **28**, 2163 (1963); *d*) R. D. Stephens and C. E. Castro, *ibid.*, **28**, 3313 (1963); *e*) C. E. Castro, E. J. Gaughan, and D. C. Owsley, *ibid.*, **31**, 4071 (1966); *f*) C. E. Castro, R. Havlin, V. K. Honwad, A. Malte, and S. Majé, *J. Am. Chem. Soc.*, **91**, 6464 (1969); *g*) J. Fujiwara, Y. Fukutani, H. Sano, K. Maruoka, and H. Yamamoto, *ibid.*, **105**, 7177 (1983).
5) *a*) K. Sonogashira, Y. Tohda, and N. Hagihara, *Tetrahedron Lett.*, **1975**, 4467; *b*) L. Casser, *J. Organometal. Chem.*, **93**, 253 (1975); *c*) H. A. Dieck and R. F. Heck, *ibid.*, **93**, 259 (1975).
6) J. A. Elvidge and R. G. Foster, *J. Chem. Soc.*, **1964**, 981.
7) O. Kruber, *Ber.*, **59**, 2752 (1926).
8) H. R. Snyder and F. J. Pilgrim, *J. Am. Chem. Soc.*, **70**, 3787 (1948).
9) H. R. Snyder, C. H. Hansh, L. Katz, S. M. Parmerter, and E. C. Spaeth, *J. Am. Chem. Soc.*, **70**, 219 (1948).
10) G. Pappalardo and T. Vitali, *Gazz. Chim. Ital.*, **88**, 1147 (1958).
11) M. S. Newman and R. Kannan, *J. Org. Chem.*, **41**, 3356 (1976).
12) J. R. Johnson and L. T. Sandborn, "Organic Syntheses," Coll. Vol. I, ed. by H. Gilman, John Wiley and Sons, Inc., New York, 1956, p. 111.
13) W. Borsche and W. Scriba, *Justus Liebig Ann. Chem.*, **541**, 283 (1938).
14) H. Kondo and S. Ishiwata, *Ber.*, **70**, 2427 (1937).
15) F. B. Danis, T. H. Vaughan, and W. M. Janney, *J. Am. Chem. Soc.*, **40**, 930 (1918).
16) G. R. Clemo and G. A. Swan, *J. Chem. Soc.*, **1948**, 198.
17) S. Okuda and M. M. Robison, *J. Org. Chem.*, **24**, 1008 (1959).