CONDENSED HETEROAROMATIC RING SYSTEMS. XXII.[1] SIMPLE AND GENERAL SYNTHESIS OF 1*H*-PYRROLOPYRIDINES

Takao Sakamoto, Chisato Satoh, Yoshinori Kondo, and Hiroshi Yamanaka*

Pharmaceutical Institute, Tohoku University, Aobayama, Aoba-ku, Sendai 980, Japan

Abstract–Four kinds of 1*H*-pyrrolopyridines having no substituent were simply and easily synthesized by the palladium-catalyzed reaction of easily available nitropyridine derivatives with (*Z*)-1-ethoxy-2-tributylstannylethene as a key reaction.

Although pyrrolopyridine derivatives have been synthesized by various methods,[2] there are relatively few reports on the synthesis of 1*H*-pyrrolopyridines having no substituent by cyclization reaction. Until today, these parent compounds were synthesized mainly by the Madelung reaction[3-8] of formylamino-methylpyridines or its equivalent derivatives. The Madelung reaction conditions, however, are relatively severe and the yields are sometimes low. Other synthetic methods of the compounds from pyridine derivatives by cyclization reaction of amino-ethynylpyridines[9,10] and by the Reissert type cyclization reaction[11,12] are known, but there is no method applicable for synthesis of all kinds of 1*H*-pyrrolopyridines. 1*H*-Pyrrolo[2,3-*c*]pyridine was obtained by the Pomeranz-Fritsch reaction of pyrrole-2-carbaldehyde, but the yield was poor.[13]

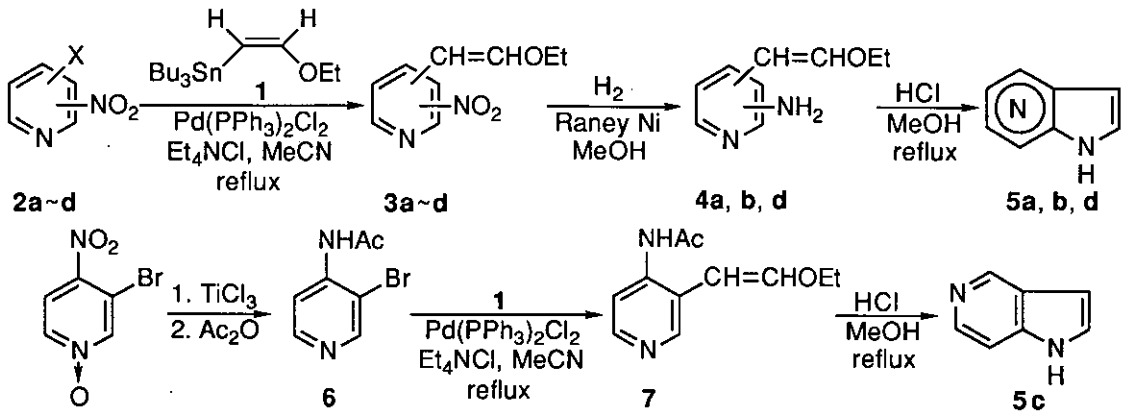
On the other hand, we have reported that (*Z*)-1-ethoxy-2-tributylstannylethene (**1**) is a versatile reagent to introduce 2-ethoxyethenyl group, an acetaldehyde equivalent group, to aromatic rings by the palladium-catalyzed reaction,[14] and that application of the reaction to 2-substituted haloaromatics provides a method to construct indoles, isocoumarins, pyrrolopyrimidines, *etc.*[1,15]

In this paper, we report the synthesis of all kinds of 1*H*-pyrrolopyridines *via* the palladium-catalyzed reaction of halonitro- or nitrotriflyloxypyridines with **1** as a key reaction.

The reaction of 2-chloro-3-nitropyridine (**2a**)[16] with **1** in the presence of dichlorobis(triphenylphosphine)palladium and tetraethylammonium chloride in acetonitrile under reflux gave (*E*)-2-(2-

ethoxyethenyl)-3-nitropyridine (**3'a**) in 96% yield. The same reaction of 4-chloro-3-nitropyridine (**2b**)[17] gave (*Z*)- (**3b**) and (*E*)-4-(2-ethoxyethenyl)-4-nitropyridines (**3'b**) in 36 and 47 % yields. Since 3-halo-2-nitropyridines are difficult to prepare, 3-hydroxy-2-nitropyridine was converted to the triflate (**2d**) which similarly reacted with **1** to give the corresponding the (*Z*)- (**3d**) and the (*E*)-3-(2-ethoxyethenyl)pyridines (**3'd**) in 74 and 14% yields.

Although the palladium-catalyzed reaction of aryl halides with **1** affords primarily (*Z*)-1-aryl-2-ethoxyethenes, the reaction of **2b, 2c**, and **2d** with **1** gave a mixture of the (*Z*)-isomers and the (*E*)-isomers as described above. As we discussed already in the preceding paper[1] concerning of the results,the (*E*)-isomers are suspected to form by isomerization of (*Z*)-isomers.



Scheme 1

Table I. Palladium-Catalyzed Reaction of **2** and **6** with **1**

Starting pyridine	Reaction time (h)	Yield (%) (*Z*)-Isomer	(*E*)-Isomer
2-chloro-3-nitropyridine (**2a**)	1.5	**3a** 0	**3'a** 96
4-chloro-3-nitropyridine (**2b**)	1.5	**3b** 36	**3'b** 47
3-bromo-4-nitropyridine (**2c**)	3	**3c** 78	**3'c** 16
3-triflyloxy-2-nitropyridine (**2d**)	1	**3d** 74	**3'd** 14
4-acetylamino-3-bromopyridine (**6**)	2.5	**7** 93	**7'** 0

The (2-ethoxyethenyl)nitropyridines (**3'a**, **3'b**, and **3d**) were catalytically hydrogenated on Raney nickel to yield the corresponding amino(2-ethoxyethenyl)pyridines (**4a,b,d**) in good yields. These compounds were easily cyclized by treatment with hydrochloric acid in methanol to the corresponding 1*H*-pyrrolopyridines (**5a,b,d**) in 87-94% yields.

Although 3-bromo-4-nitropyridine (**2c**)[18] reacts analogously with **1** to give (*Z*)-isomer (**3c**: 78%)

and (*E*)-isomer (**3'c**: 16%), the compounds are unstable to use in the next step. Then, 3-bromo-4-nitropyridine 1-oxide was reduced with titanium trichloride[19] to 4-amino-3-bromopyridines which were transformed to the acetyl derivative (**6**). The palladium-catalyzed reaction of **6** with **1** gave stable (*Z*)-4-acetylamino-3-(2-ethoxyethenyl)pyridine (**7**) in 93% yield, which was transformed into 1*H*-pyrrolo[3,2-*c*]pyridine (**5c**) in 90% yield.

In this paper, we described the cyclization of either the (*E*)- or (*Z*)-amino(2-ethoxyethenyl)pyridines obtained from the corresponding nitro derivatives which were obtained as the main products by the palladium-catalyzed reaction of **2** with **1**. Since the cyclization to the 1*H*-pyrrolopyridines without separation of (*Z*)- and (*E*)-amino(2-ethoxyethenyl)pyridines would be possible, the method is simple and general one to synthesize all kinds of 1*H*-pyrrolopyridines.

EXPERIMETNTAL

Melting points were determined in capillary tubes and are uncorrected. Ir spectra were recorded on a JASCO IRA-1 spectrophotometer. ^{1}H Nmr spectra were recorded on a JEOL PMX-60 (60 MHz) using tetramethylsilane as an internal standard. Chemical shifts are expressed in δ (ppm) values, and coupling constants are expressed in hertz (Hz). The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, dd=double doublet, and br=broad. Ms and high resolution ms (HRms) were recorded on a JEOL JMS-DX303 spectrometer. Elemental analyses were performed by the staff of the Central Analysis Room of Pharmaceutical Institute, Tohoku University.

4-Amino-3-bromopyridine: A mixture of 3-bromo-4-nitropyridine 1-oxide[20] (4.38 g, 20 mmol), 20% aq. $TiCl_3$ (123 g, 160 mmol), AcOH (50 ml), and H_2O (50 ml) was stirred at room temperature for 25 h. The mixture was basified with 3N NaOH and filtered through a Cerite® pad. The filtrate was continuously extracted with $CHCl_3$. The $CHCl_3$ extract was dried over $MgSO_4$ and evaporated. *The residue was recrystallized from Et_2O-hexane to give colorless needles. Yield 2.60 g* (75%). mp 181-182°C. Lit.,[21] mp 181-182.5°C.

2-Nitro-3-trifluoromethanesulfonyloxypyridine (2d): A mixture of 3-hydroxy-2-nitropyridine[22] (0.98 g, 7 mmol) and 60% NaH (0.34 g, 8.5 mmol) in dry C_6H_6 (20 ml) was stirred at room temperature for 1 h. Then trifluoromethanesulfonic anhydride (2.17 g, 7.7 mmol) in C_6H_6 (20 ml) was added. The whole mixture was refluxed for 60 h. After removal of the solvent, the residue was partitioned between H_2O and $CHCl_3$. The $CHCl_3$ layer was dried over $MgSO_4$ and evaporated. The residue was purified by SiO_2 column chromatography using AcOEt-hexane (1:1) as an eluent to gave a colorless liquid. Yield 0.99 g (52%). ^{1}H Nmr ($CDCl_3$): 7.97 (1H, dd, *J*=3, 4), 8.00 (1H, dd, *J*=2, 3), 8.67 (1H, dd, *J*=2, 4); ms (*m/z*): 271 (M^+); HRms calcd for $C_6H_3N_2O_5F_3S$: 271.9715; found:

271. 9716.

Palladium-Catalyzed Reaction of Halo- and Triflyloxynitropyridines with 1 (General Procedure): A mixture of a pyridine derivative (**2a-d** or **6**) (3 mmol), **1** (1.30 g, 3.6 mmol), Et_4NCl (0.5 g, 3 mmol) and $Pd(PPh_3)_2Cl_2$ (80 mg, 0.1 mmol) in MeCN (10 ml) was refluxed for the time shown in Table I. After removal of the solvent, the residue was mixed with $CHCl_3$ and H_2O. The mixture was filtered through a Cerite® pad. The aqueous layer was extracted with $CHCl_3$. The $CHCl_3$ extract was dried over $MgSO_4$ and evaporated. The residue was purified by SiO_2 column chromatography using AcOEt-hexane (1:9) for the case of the nitropyridines and AcOEt-hexane (1:1) for the case of the acetylaminopyridine.

(*E*)-2-(2-Ethoxyethenyl)-3-nitropyridine (3'a): Yellow needles (Et_2O-hexane). mp 103-104°C. ^1H Nmr ($CDCl_3$): 1.40 (3H, t, *J*=7), 4.07 (2H, q, *J*=7), 6.60 (1H, d, *J*=12), 7.12 (1H, dd, *J*=5, 8), 8.00 (1H, d, *J*=12), 8.17 (1H, dd, *J*=2, 8), 8.58 (1H, dd, *J*=2, 5). *Anal.* Calcd for $C_9H_{10}N_2O_3$: C, 55.67; H, 5.19; N, 14.43. Found: C, 55.73; H, 5.22; N, 14.58.

(*Z*)-4-(2-Ethoxyethenyl)-3-nitropyridine (3b): Yellow liquid. ^1H Nmr ($CDCl_3$): 1.40 (3H, t, *J*=7), 4.03 (2H, q, *J*=7), 5.83 (1H, d, *J*=7), 6.63 (1H, d, *J*=7), 8.10 (1H, d, *J*=5), 8.73 (1H,d, *J*=5), 9.00 (1H, s); ms (*m/z*): 194 (M^+); HRms calcd for $C_9H_{10}N_2O_3$: 194.0691; found: 194.0672.

(*E*)-4-(2-Ethoxyethenyl)-3-nitropyridine (3'b): Yellow needles (Et_2O-hexane). mp 53-54°C. ^1H Nmr ($CDCl_3$): 1.40 (3H, t, *J*=7), 4.00 (2H, q, *J*=7), 6.47 (1H, d, *J*=13), 7.33 (1H, d, *J*=13), 7.40 (1H, d, *J*=5), 8.50 (1H, d, *J*=5), 9.07 (1H, s). *Anal.* Calcd for $C_9H_{10}N_2O_3$: C, 55.67; H, 5.19; N, 14.43. Found: C, 55.62; H, 5.08; N, 14.30.

(*Z*)-3-(2-Ethoxyethenyl)-4-nitropyridine (3c): Yellow liquid. ^1H Nmr ($CDCl_3$): 1.40 (3H, t, *J*=7), 4.03 (2H, q, *J*=7), 5.52 (1H, d, *J*=7), 6.42 (1H, d, *J*=7), 7.25 (1H, d, *J*=5), 8.20 (1H,d, *J*=5), 9.27 (1H, s); ms (*m/z*): 194 (M^+); HRms calcd for $C_9H_{10}N_2O_3$: 194.0691; found: 194.0688.

(*E*)-3-(2-Ethoxyethenyl)-4-nitropyridine (3'c): Yellow liquid. ^1H Nmr ($CDCl_3$): 1.40 (3H, t, *J*=7), 3.98 (2H, q, *J*=7), 5.98 (1H, d, *J*=13), 7.08 (1H, d, *J*=13), 7.25 (1H, d, *J*=5), 8.27 (1H,d, *J*=5), 8.57 (1H, s); ms (*m/z*): 194 (M^+); HRms calcd for $C_9H_{10}N_2O_3$: 194.0691; found: 194.0689.

(*Z*)-3-(2-Ethoxyethenyl)-2-nitropyridine (3d): Yellow liquid. ^1H Nmr ($CDCl_3$): 1.33 (3H, t, *J*=7), 4.05 (2H, q, *J*=7), 5.43 (1H, d, *J*=7), 6.45 (1H, d, *J*=7), 7.45 (1H, dd, *J*=4, 8), 8.25 (1H,dd, *J*=2, 4), 8.25 (1H, dd, *J*=2, 8); ms (*m/z*): 194 (M^+); HRms calcd for $C_9H_{10}N_2O_3$: 194.0691; found: 194.0710.

(*E*)-3-(2-Ethoxyethenyl)-2-nitropyridine (3'd): Yellow liquid. ^1H Nmr ($CDCl_3$): 1.37 (3H, t, *J*=7), 3.97 (2H, q, *J*=7), 6.07 (1H, d, *J*=13), 7.08 (1H, d, *J*=13), 7.50 (1H, dd, *J*=5, 8), 7.92 (1H,dd, *J*=2, 8), 8.28 (1H, dd, *J*=2, 5); ms (*m/z*): 194 (M^+); HRms calcd for $C_9H_{10}N_2O_3$: 194.0691; found:

194.0694.

(*Z*)-4-Acetylamino-3-(2-ethoxyethenyl)pyridine (7): Colorless liquid. Ir ($CHCl_3$): 3340 cm^{-1}; ^1H Nmr ($CDCl_3$): 1.36 (3H, t, *J*=7), 2.20 (3H, s), 4.07 (2H, q, *J*=7), 5.28 (1H, d, *J*=7), 6.33 (1H, d, *J*=7), 7.8-8.4 (1H, br), 8.13 (1H, d, *J*=5), 8.37 (1H,d, *J*=5), 8.50 (1H, s); ms (*m/z*): 206 (M^+); HRms calcd for $C_{11}H_{14}N_2O_2$: 206.1054; found: 206.1051.

Catalytic Hydrogenation of 2-Ethoxyethenylnitropyridine (3) (General Procedure): A mixture of a 2-ethoxyethenylnitropyridine (**3'a**, **3'b**, or **3d**) and W-2 Raney Ni (1 ml) in MeOH (40 ml) was hydrogenated under atmospheric pressure of hydrogen. After filtration of the catalyst, the filtrate was evaporated in vacuo. The residue was purified by SiO_2 column chromatography.

(*E*)-3-Amino-2-(2-ethoxyethenyl)pyridine (4a): Colorless liquid (elution with AcOEt-hexane (1:1)). Yield 80%. Ir ($CHCl_3$): 3350, 3240 cm^{-1}; ^1H Nmr ($CDCl_3$): 1.33 (3H, t, *J*=7), 3.2-4.3 (2H, br), 3.95 (2H, q, *J*=7), 5.90 (1H, d, *J*=12), 6.88 (1H, dd, *J*=1, 3), 6.95 (1H, dd, *J*=1, 4), 7.50 (1H, d, *J*=12), 7.95 (1H, dd, *J*=3, 4); ms (*m/z*): 164 (M^+); HRms calcd for $C_9H_{12}N_2O$: 164.0950; found: 164.0953.

(*E*)-3-Amino-4-(2-ethoxyethenyl)pyridine (4b): Colorless needles (elution with AcOEt; recrystallized from Et_2O). Yield 89%. mp 80-81°C. Ir ($CHCl_3$): 3400, 3250; ^1H Nmr ($CDCl_3$): 1.33 (3H, t, *J*=7), 3.4-4.3 (2H, br), 3.93 (2H, q, *J*=7), 5.73 (1H, d, *J*=12), 6.98 (1H, d, *J*=12), 7.00 (1H, d, *J*=5), 7.93 (1H, d, *J*=5), 8.00 (1H, s). *Anal.* Calcd for $C_9H_{12}N_2O$: C, 65.83; H, 7.37; N, 17.06. Found: C, 65.66; H, 7.15; N, 16.91.

(*Z*)-2-Amino-3-(2-ethoxyethenyl)pyridine (4d): Colorless liquid (elution with AcOEt-hexane (1:4)). Yield 78%. Ir ($CHCl_3$): 3400, 3250 cm^{-1}; ^1H Nmr ($CDCl_3$): 1.30 (3H, t, *J*=7), 3.95 (2H, q, *J*=7), 4.1-5.0 (2H, br), 5.05 (1H, d, *J*=7), 6.22 (1H, d, *J*=7), 6.60 (1H, dd, *J*=5, 6), 7.75 (1H, dd, *J*=2, 6), 7.87 (1H,dd, *J*=2, 5); ms (*m/z*): 164 (M^+); HRms calcd for $C_9H_{12}N_2O$: 164.0950; found: 164.0969.

Cyclization of Amino(2-ethoxyethenyl)pyridines to 1*H*-Pyrrolopyridines (General Procedure): A mixture of an amino- (**4a**, **b**, **d**) or acetylamino(2-ethoxyethenyl)pyridine (**7**) (2.5 mmol) and conc. HCl (0.5 ml) in MeOH (10 ml) was refluxed for 1-2 h. After evaporation of the solvent, the residue was basified with solid K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over $MgSO_4$. The crude product obtained from the $CHCl_3$ extract was purified by recrystallization.

Pyrrolo[3,2-*b*]pyridine (5a): Colorless needles (AcOEt-hexane). Yield 88%. mp 125-126°C. Lit.,[4] mp 127-128°C. Ir ($CHCl_3$): 3460 cm^{-1}; ^1H Nmr ($CDCl_3$): 6.72 (1H, dd, *J*=2, 3), 7.08 (1H, dd *J*=5, 8), 7.50 (1H, dd, *J*=2, 3), 7.72 (1H, dd, *J*=1, 8), 8.48 (1H, dd, *J*=1, 5), 10.2-11.3 (1H, br).

Pyrrolo[2,3-*c*]pyridine (5b): Colorless needles (AcOEt-hexane). Yield 87%. mp 137-138°C. Lit.,[23] mp 136-138°C. Ir ($CHCl_3$): 3460 cm^{-1}; ^1H Nmr ($CDCl_3$): 6.57 (1H, dd, *J*=1, 3), 7.50 (1H, d

J=3), 7.60 (1H, d, *J*=5), 8.28 (1H, d, *J*=5), 8.88 (1H, s), 10.1-11.8 (1H, br).

Pyrrolo[3,2-*c*]pyridine (5c): Colorless needles ($CHCl_3$-hexane). Yield 90%. mp 110-111°C. Lit.,[6] mp 111.5-112.5°C. Ir ($CHCl_3$): 3460 cm^{-1}; ^1H Nmr ($CDCl_3$): 6.63 (1H, dd, *J*=1, 3), 7.30 (1H, d, *J*=6), 7.36 (1H, d, *J*=3), 8.27 (1H, d, *J*=6), 9.00 (1H, s), 10.7-12.3 (1H, br).

Pyrrolo[2,3-*b*]pyridine (5d): Colorless needles (hexane). Yield 94%. mp 104-106°C. Lit.,[5] mp 105-106°C. Ir ($CHCl_3$): 3450 cm^{-1}; ^1H Nmr ($CDCl_3$): 6.45 (1H, dd, *J*=1, 4), 7.03 (1H, dd, *J*=6, 9), 7.33 (1H, d, *J*=4), 7.93 (1H, dd, *J*=1, 9), 8.23 (1H, dd, *J*=1, 6), 11.5-12.7 (1H, br).

REFERENCES

1. Part XXI: T. Sakamoto, C. Satoh, Y. Kondo, and H. Yamanaka, *Chem. Pharm. Bull.*, in press.
2. L. N. Yakhontov and A. A. Prokopov, *Russ. Chem. Rev.*, 1980, **49**, 428.
3. G. R. Clemo and G. A. Swan, *J. Chem. Soc.*, 1945, 603.
4. G. R. Clemo and G. A. Swan, *J. Chem. Soc.*, 1948, 198.
5. M. M. Robison and R. L. Robison, *J. Am. Chem. Soc.*, 1955, **77**, 457.
6. S. Okuda and M. M. Robison, *J. Org. Chem.*, 1959, **24**, 1008.
7. S. Archer, *J. Org. Chem.*, 1965, **30**, 2531.
8. R. Herbert and D. G. Wibberley, *J. Chem. Soc. (C)*, 1969, 1505.
9. J. Reisch, *Chem. Ber.*, 1964, **97**, 2718.
10. T. Sakamoto, Y. Kondo, S. Iwashita, and H. Yamanaka, *Chem. Pharm. Bull.*, 1987, **35**, 1823.
11. R. Fontan, C. Galvez, and P. Viladoms, *Heterocycles*, 1981, **16**, 1473.
12. T. Sakamoto, Y. Kondo, and H. Yamanaka, *Chem. Pharm. Bull.*, 1986, **34**, 2362.
13. W. Herz and S. Tocker, *J. Am. Chem. Soc.*, 1955, **77**, 6355.
14. T. Sakamoto, Y. Kondo, A. Yasuhara, and H. Yamanaka, *Heterocycles*, 1990, **31**, 219.
15. T. Sakamoto, Y. Kondo, A. Yasuhara, and H. Yamanaka, *Tetrahedron*, 1991, **47**, 1877.
16. A. H. Berrie, G. T. Newbold, and F. S. Spring, *J. Chem. Soc.*, 1952, 2042.
17. M. F. Reich, P. F. Fabio, V. J. Lee, N. A. Kuck, and R. T. Testa, *J. Med. Chem.*, 1989, **32**, 2474.
18. Z. Talik and T. Talik, *Rocz. Chem.*, 1962, **36**, 545 [*Chem. Abstr.*, 1962, **57**, 12421a].
19. M. Somei, K. Kato, and S. Inoue, *Chem. Pharm. Bull.*, 1980, **28**, 2515.
20. O. S. Tee and M. Paventi, *Can. J. Chem.*, 1983, **61**, 1064.
21. W. W. Paudler and M. V. Jovanovic, *J. Org. Chem.*, 1983, **48**, 1064.
22. R. C. DeSelms, *J. Org. Chem.*, 1968, **33**, 478.
23. V. O. Sus and K. Moller, *Liebigs Ann. Chem.*, 1956, **599**, 233.

Received, 24th July, 1992