

CYCLIZATION REACTION OF *N*-SILYL-1-AZAALLYL ANIONS WITH MICHAEL ACCEPTORS AS A NEW SYNTHETIC METHOD OF 2,3,5,6-TETRA- and 2,3,6-TRISUBSTITUTED PYRIDINES

Takeo Konakahara,* Naoki Sugama, Asuka Yamada, Akikazu Kakehi,[†] and Norio Sakai

Department of Industrial Chemistry, Faculty of Science and Technology, Science University of Tokyo, Noda, Chiba 278-8510, Japan;
e-mail konaka@ci.noda.sut.ac.jp

[†]Department of Chemistry and Material Engineering, Faculty of Engineering, Shinshu University, Wakasato, Nagano 380-8553, Japan

Abstract- Fifteen kinds of 2,3,5,6-tetra- or 2,3,6-trisubstituted pyridines were synthesized from *N*-silyl-1-azaallyl anions and Michael acceptors in excellent to moderate yields.

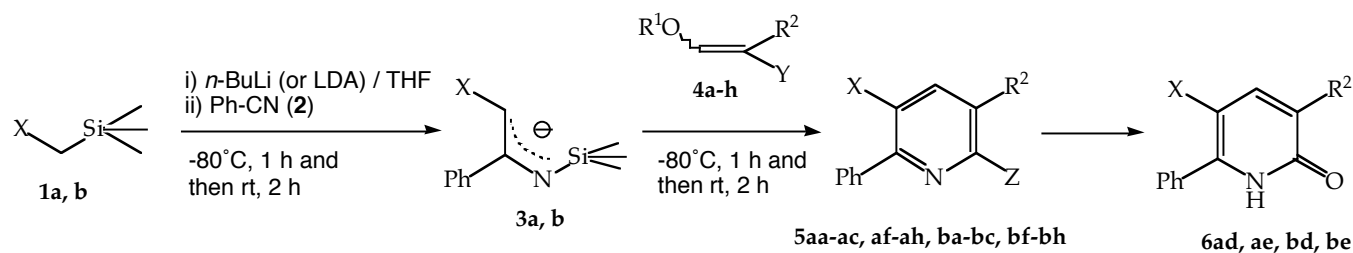
INTRODUCTION

Although much attention has been received on the chemistry of 1-azaallyl anions,¹ most of them have been utilized for the carbon-carbon bond formation. Utility of anions bearing a trialkylsilyl group on the nitrogen for the synthesis of heterocyclic compounds such as pyridine derivatives has been almost unexplored. The pyridine nucleus is a major component of a variety of natural products and drugs.² Recently we have developed an efficient method for the synthesis of 2,3,4,6-tetra- or 2,3,4,5,6-pentasubstituted pyridine derivatives from *N*-silyl-1-azaallyl anions³⁻⁵ and 1,3-diphenyl-2-propen-1-one⁶ or perfluoro(2-methyl-2-pentene).⁷ The *N*-silyl-1-azaallyl anions, which are easily generated from the corresponding aromatic nitriles and α -silylcarbanions, show ambident reactivity at the nitrogen and carbon atoms and can be utilized as a versatile building block for the synthesis of *N*-heterocyclic compounds.⁶⁻¹¹ We wish to report here a one-pot synthesis route of 2,3,5,6-tetra- and 2,3,6-trisubstituted pyridine derivatives (**5**) (or **6**) by the reaction of *N*-silyl-1-azaallyl anions (**3**) with 8 kinds of Michael acceptors (**4a-h**).

RESULTS AND DISCUSSION

α -Silylcarbanions, derived from the α -functionalized alkylsilanes (**1a,b**) in the presence of butyllithium (*n*-BuLi) or LDA,¹² reacted with benzonitrile (**2**) at -80°C in tetrahydrofuran (THF) to give the 3-(3-methyl-5-isoxazolyl)-2-phenyl- or 2-phenyl-3-(2-pyridyl)-*N*-trimethylsilyl-1-azaallyl anion, (**3a**) or (**3b**), as previously reported.^{3, 4} The *N*-silyl-1-azaallyl anions (**3a,b**) were treated with Michael acceptors (**4a-h**) (mixtures of *E* / *Z*-isomers) for 1 h at -80°C, and then for 2 h at room temperature to give the pyridine derivatives (**5**) or (**6**) as shown in Scheme 1 and Table 1. For example, the reaction of **3a** with 3-acetyl-4-methoxy-3-buten-2-one (**4a**) or methyl 2-acetyl-3-methoxypropenoate (**4b**) gave 3-acetyl-2-methyl-5-(3-

methyl-5-isoxazolyl)-6-phenylpyridine (**5aa**) or methyl 2-methyl-5-(3-methyl-5-isoxazolyl)-6-phenyl-nicotinate (**5ab**) in excellent yields (90 and 91%, respectively). Similarly, 4-ethoxy-1,1,1-trifluoro-3-



Scheme 1

Table 1. Synthesis of 2,3,5,6-tetra- or 2,3,6-trisubstituted pyridines (**5**) or (**6**) from *N*-silyl-1-azaallyl anions (**3**)^a

1, 3	X ^b	4	R ¹	R ²	Y	Product	Z	Yield of 5 or 6 (%) ^c
a	5-MIX	a	Me	COMe	COMe	5aa	Me	90
a	5-MIX	b	Me	COOMe	COMe	5ab	Me	91
a	5-MIX	c	Et	H	COCF ₃	5ac	CF ₃	89
a	5-MIX	d	Et	COOEt	COOEt	6ad		62
a	5-MIX	e	Me	H	COOMe	6ae		11(27)
a	5-MIX	f	Et	COOEt	CN	5af	NH ₂	68
a	5-MIX	g	Me	H	CN	5ag	NH ₂	2[46] ^{d,e}
a	5-MIX	h	Et	CN	CN	5ah	NH ₂	10[60] ^{d,e}
b	2-Py	a	Me	COMe	COMe	5ba	Me	58-60
b	2-Py	b	Me	COOMe	COMe	5bb	Me	44
b	2-Py	c	Et	H	COCF ₃	5bc	CF ₃	33
b	2-Py	d	Et	COOEt	COOEt	6bd		39
b	2-Py	e	Me	H	COOMe	6be		16 ^f
b	2-Py	f	Et	COOEt	CN	5bf	NH ₂	45
b	2-Py	g	Me	H	CN	5bg	NH ₂	0[nd] ^{f, g}
b	2-Py	h	Et	CN	CN	5bh	NH ₂	25[nd] ^{f, g}

^a Molar ratio, **1** : *n*-BuLi : **2** : **4** = 1 : 1 : 1 : 1; stirred for 1 h at -80 °C and then for 2 h (or 24 h for the reaction of **3b**) at room temperature in THF, unless otherwise indicated; LDA was used in the reaction of **1b** in spite of *n*-BuLi.

^b 5-MIX: the 5-(3-methyl)isoxazolyl group

^c Yield of the pure product isolated and that determined by ¹H NMR in parentheses.

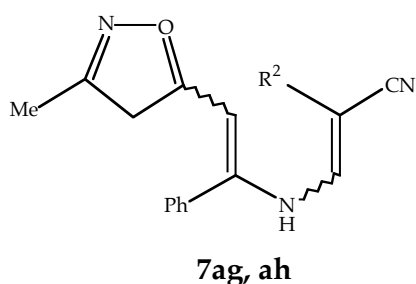
^d Stirred for 1 h at -80 °C and then for 2 h under reflux in THF.

^e Yield of the corresponding *N*-1,4-adduct (**7**) in brackets.

^f Considerable amount of 2-phenacylpyridine³ was obtained.

^g nd: not determined

buten-2-one (**4c**) gave 3-(3-methyl-5-isoxazolyl)-2-phenyl-6-trifluoromethylpyridine (**5ac**) in 89% yield. Furthermore, both ethyl 3-ethoxy-2-ethoxycarbonyl-2-propenoate (**4d**) and methyl 3-methoxypropenoate (**4e**) gave the corresponding 2-pyridone derivatives (**6ad**) and (**6ae**). The yield of **6ad** was good (62%) but that of **6ae** was moderate (27% by ^1H NMR). On the other hand, Michael acceptors (**4f-h**), possessing a cyano group as the substituent Y, afforded 2-aminopyridines (**5af-ah**) in good to poor yields as shown in Table 1. The ethoxycarbonyl group as R^2 accelerates the yield of **5af** (68%). Contrary to our expectation, 3-methoxypropenenitrile (**4g**) and 2-cyano-3-methoxypropenenitrile (**4h**) did not give the pyridines as major products but gave the corresponding N-1,4-adducts (**7ag, 7ah**; 46, 60% yields, respectively). These compounds were formed by attack of the nitrogen atom of the anion (**3a**) to the β -carbon atom of **4g** or **4h**. All attempts to transform **7ah** to the corresponding 2,3,4,5-tetrasubstituted pyridine, however, resulted in failure under various reaction conditions. The compound (**7ah**) was recovered from the reaction mixture. The result suggests that **7ah** was not a true intermediate of the pyridine product, and that the pyridine ring of **5** (or **6**) may be constructed by the C-1,4-addition reaction as discussed below. The acetyl and the



trifluoroacetyl groups as substituent Y cyclized more easily to give **5** than the alkoxy carbonyl and the cyano groups did. The electron-withdrawing group is preferable as substituent R^2 in the formation of **5**.

The reaction of 2-phenyl-3-(2-pyridyl)-*N*-trimethylsilyl-1-azaallyl anion (**3b**) also gave the corresponding pyridine derivatives (**5** or **6**) in good to poor yields except for **5bg** (Table 1). The reactivity of **3b** is lower than that of **3a** and a large amount of the unreacted **3b** was recovered as 2-phenacylpyridine from the reaction mixture after work-up.

The structure of **5bf** was confirmed by a single crystal X-Ray structural analysis¹³ and the structures of the other products were deduced by a comparison of the spectroscopic data with those of **5bf**. ORTEP¹⁴ drawing is shown in Figure 1. The structure of **5bf** is ethyl 2-amino-6-phenyl-5-(2-pyridyl)nicotinate contrary to our preliminary report,¹⁵ in which we expected an ambiguous structure of the product to be the corresponding 4-aminopyridine derivative.

The structures of **7ag** and **7ah** were determined not only by their spectral properties but also by chemical transformation of **7ag** to (3-methyl-5-isoxazolyl)methyl phenyl ketone by acidic hydrolysis, as previously reported.¹⁵

According to the frontier orbital theory, a reaction is apt to occur on an atom in which the coefficient of the frontier molecular orbital (FMO) is large. Therefore, FMO coefficients of **3a**, **3b**, **4a**, **4f**, and **4g** were calculated by PM3 method,¹⁶ and some of them are shown in Tables 2 and 3. In the case of *N*-silyl-1-azaallyl anion (**3b**), the HOMO coefficient (0.637) of the C3 atom is larger than that of the N1 atom (-0.459); and the LUMO coefficient (-0.702) of the C4 atom in **4f** is larger than that of the C2 atom (0.288 or 0.146).

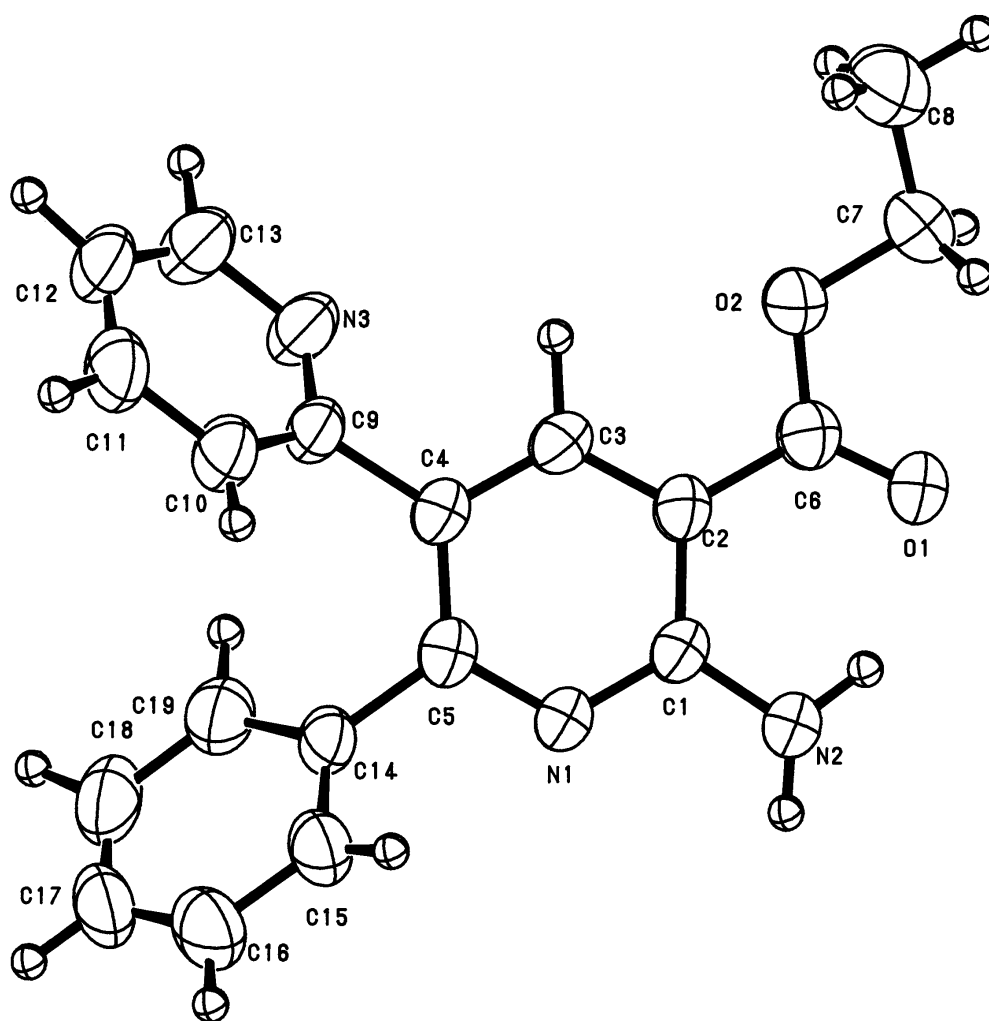


Figure 1. ORTEP¹⁴ drawing of ethyl 2-amino-6-phenyl-5-(2-pyridyl)nicotinate (**5bf**)

Table 2. Coefficients^a for HOMO of *N*-silyl-1-azaallyl anions (**3a,b**)

3	HOMO coefficients	
	N1	C3
a	0.249	-0.623
b	-0.459	0.637

^a Calculated by PM3 method.¹⁶

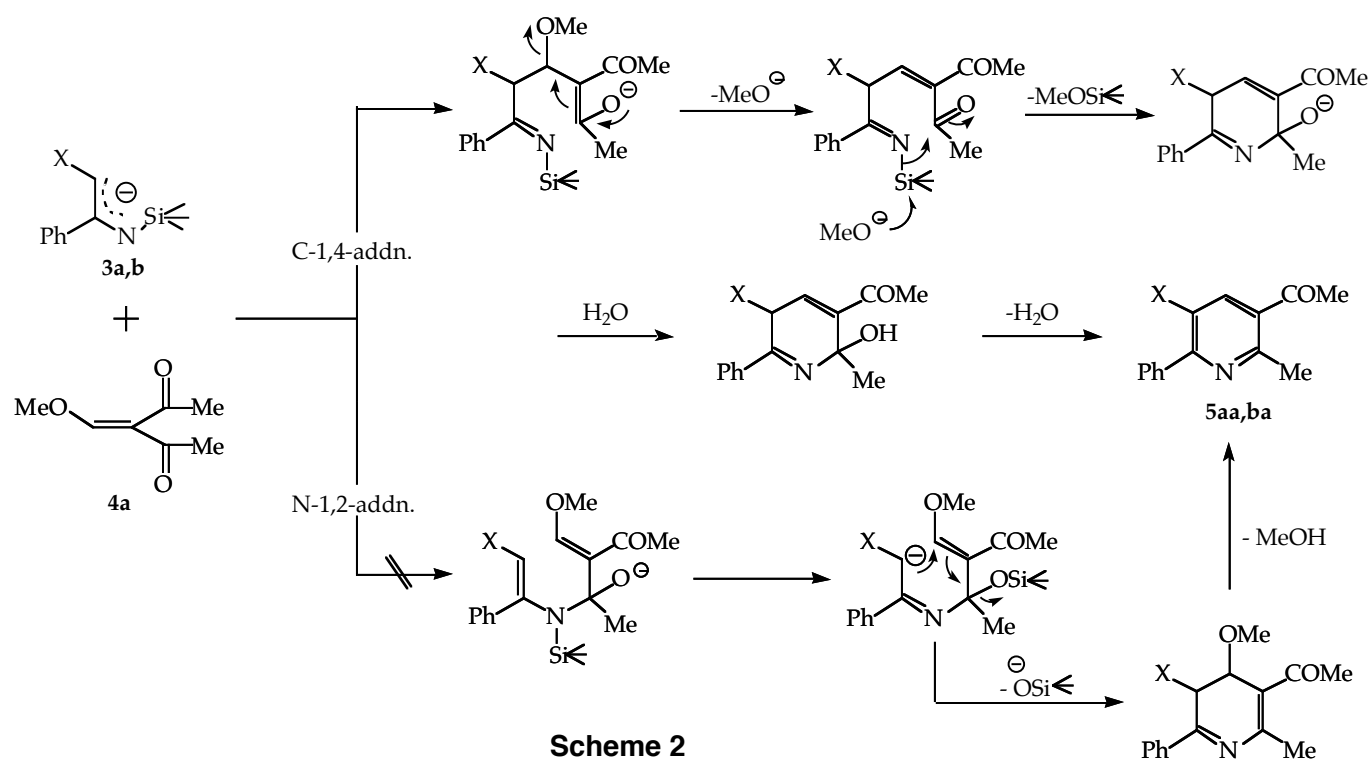
Table 3. Coefficients^a for LUMO of Michel acceptors (**4a,f,g**)

4	LUMO coefficients		
	C2 ^b (COR)	C2 ^b (CN)	C4
a	0.050	--	0.659
f	0.288	0.146	-0.702
g	--	-0.282	0.680

^a Calculated by PM3 method.¹⁶ ^b C2 denotes the carbonyl carbon or the cyano carbon.

Therefore, bond formation between the C3 atom of **3b** and the C4 atom of **4f** (the C-1,4-addition) is preferred to the alternative N-1,2-addition in the formation of **5bf** (Scheme 2). The other reaction mechanisms, such as C-1,2- and N-1,4-additions, should be excluded. Indeed, the calculated prediction is in good agreement with the experimental results, which were confirmed by X-Ray crystallography and the reactivity of **7ah** against cyclization. In addition, there are many reports about the C-1,4-addition.^{17, 18} Further mechanistic investigation is in progress.

Miyajima and his co-workers have reported the synthesis of pyridine derivatives from *N*-*t*-butylimines and **4d**, **4f**, or **4h** at an elevated temperature.¹⁷ In comparison with their method, the present method has the advantages of the lower reaction temperatures, the shorter reaction times, and the higher yields of pyridines. The present method, however, is of no advantage to their method in the case of **4g** or **4h**.¹⁸



EXPERIMENTAL

All mps (Yanagimoto micro-melting point apparatus) are uncorrected. IR spectra were taken on a JEOL IR-5300 spectrophotometer. ¹H NMR spectra were determined with a JNM PMX-60SI, FX-90Q, or AL-300 spectrometer for solutions in CDCl₃ or DMSO-*d*₆. Chemical shifts are reported in δ values (internal standard Me₄Si). ¹⁹F NMR spectra were determined with a JNM FX-90Q spectrometer for solutions in CDCl₃, and chemical shifts are also reported in δ values (negative for upper-field than an internal standard, CFCl₃). Low and high resolution MS were recorded with a JMS-700 double focusing mass spectrometer at 70 eV. Elemental analyses were performed at the Instrumental Analysis Center in Science University of Tokyo.

Materials: 3-Methyl-5-trimethylsilylmethylisoxazole⁵ (**1a**), 2-(trimethylsilylmethyl)pyridine³ (**1b**), 3-acetyl-4-methoxy-3-buten-2-one¹⁰ (**4a**), methyl 2-acetyl-3-methoxy-2-propenoate¹⁹ (**4b**) and 1,1,1-

trifluoro-4-ethoxy-3-buten-2-one²⁰ (**4c**) were prepared by the methods reported previously. All other reagents were obtained from commercial source.

Synthesis of pyridine derivatives (5) and (6); General procedure: All pyridine derivatives (**5**) and (**6**) were prepared according to the procedure given below. As an example, the synthesis of 3-acetyl-2-methyl-5-(3-methyl-5-isoxazolyl)-6-phenylpyridine (**5aa**) was shown. A 15% solution of *n*-BuLi (12.5 mL, 20 mmol) in hexane was added to a solution of 3-methyl-5-trimethylsilylmethylisoxazole (**1a**) (3.41 g, 20 mmol) in THF (50 mL) at -80°C with stirring under nitrogen atmosphere (in the reaction of **1b**, LDA was used instead of *n*-BuLi). After 1 h stirring at the same temperature, benzonitrile (**2**) (2.06 g, 20 mmol) was slowly added to the solution, and the mixture was stirred for 1 h at -80°C and then for 2 h at rt to give the 3-(3-methyl-5-isoxazolyl)-2-phenyl-*N*-trimethylsilyl-1-azaallyl anion (**3a**). After cooling to -80°C, methyl 2-acethyl-3-methoxy-2-propenoate (**4a**) (2.84 g, 20 mmol) was slowly added to the solution of **3a**, and the mixture was stirred for 1 h at -80°C and then for 2 h at rt. The resulting mixture was finally quenched with saturated aqueous NH₄Cl solution (50 mL) at 0°C, and extracted with ether. The organic extracts were dried (Na₂SO₄) and evaporated *in vacuo*. The crude product was recrystallized from acetone-hexane (or chromatographed on silica gels eluting with CHCl₃, CH₂Cl₂, or a mixture of them, if necessary, in the purification of some of the other compounds) to afford pure **5aa** (5.26 g, 90%) (see Table 1). mp 154.6-155.1°C; IR(KBr) $\nu_{\max}/\text{cm}^{-1}$ 1695($\nu_{\text{C=O}}$); ¹H NMR (CDCl₃) δ 2.10(3H, s, Isoxazolyl-CH₃), 2.56(3H, s, Py-CH₃), 2.71(3H, s, COCH₃), 5.21(1H, s, Isoxazolyl-H), 7.12(5H, m, Ph-H), 8.07 (1H, s, Py-H); MS *m/z* 292(M⁺, 100%); *Anal.* Calcd for C₁₈H₁₇N₃O₂: C, 73.95; H, 5.52; N, 9.58. Found: C, 73.74; H, 5.24; N, 9.38.

Methyl 2-methyl-5-(3-methyl-5-isoxazolyl)-6-phenylnicotinate (5ab): mp 137.7-138.3°C (from acetone-ether); IR(KBr) $\nu_{\max}/\text{cm}^{-1}$ 1730($\nu_{\text{C=O}}$); ¹H NMR(CDCl₃) δ 2.10(3H, s, Isoxazolyl-CH₃), 2.79 (3H, s, Py-CH₃), 3.79(3H, s, COOCH₃), 5.27(1H, s, Isoxazolyl-H), 7.14(5H, m, Ph-H), 8.31(1H, s, Py-H); MS *m/z* 267(M⁺, 100%); *Anal.* Calcd for C₁₈H₁₇N₃O₃: C, 70.12; H, 5.28; N, 9.09. Found: C, 70.04; H, 5.09; N, 8.99.

3-(3-Methyl-5-isoxazolyl)-2-phenyl-6-trifluoromethylpyridine (5ac): mp 75.7-76.2°C (from ether-hexane); IR(KBr) $\nu_{\max}/\text{cm}^{-1}$ 1190-1105($\nu_{\text{C-F}}$); ¹H NMR(CDCl₃) δ 2.10(3H, s, Isoxazolyl-CH₃), 5.30(1H, s, Isoxazolyl-H), 7.13(5H, m, Ph-H), 7.40(1H, d, *J* = 7.7 Hz, Py-H), 7.96(1H, d, *J* = 7.7 Hz, Py-H); ¹⁹F NMR(CDCl₃) δ -68.6(m, CF₃); MS *m/z* 304 (M⁺, 83%), 263(100%); *Anal.* Calcd for C₁₆H₁₁N₂OF₃: C, 63.16; H, 3.64; N, 9.21. Found: C, 63.07; H, 3.66; N, 9.04.

3-Ethoxycarbonyl-5-(3-methyl-5-isoxazolyl)-6-phenyl-2-pyridone (6ad): mp 207.0-207.9°C (from acetone-hexane); IR(KBr) $\nu_{\max}/\text{cm}^{-1}$ 2910, 1740[$\nu_{\text{C=O}}$ (ester)], 1648($\nu_{\text{C=O}}$); ¹H NMR(DMSO-*d*₆) δ 1.26(3H, t, *J* = 7.1 Hz, CH₂CH₃), 2.02(3H, s, Isoxazolyl-CH₃), 4.14(2H, q, *J* = 7.1 Hz, CH₂CH₃), 5.37(1H, s, Isoxazolyl-H), 7.22(5H, m, Ph-H), 8.04(1H, s, Py-H), 12.16(1H, br s, NH); MS *m/z* 324(M⁺, 100%); *Anal.* Calcd for C₁₈H₁₆N₂O₄: C, 66.66; H, 4.97; N, 8.64. Found: C, 66.90; H, 5.09; N, 8.51.

5-(3-Methyl-5-isoxazolyl)-6-phenyl-2-pyridone (6ae): mp 215.0-215.5°C (from acetone-hexane); IR(KBr) $\nu_{\max}/\text{cm}^{-1}$ 2920, 1648($\nu_{\text{C=O}}$); ^1H NMR(DMSO- d_6) δ 2.13(3H, s, Isoxazolyl- CH_3), 5.56(1H, s, Isoxazolyl-H), 6.47 (1H, d, $J = 8.7$ Hz, Py-H), 7.21(5H, m, Ph-H), 7.79(1H, d, $J = 8.7$ Hz, Py-H), 11.56(1H, br s, NH); MS m/z 252(M^+ , 100%); *Anal.* Calcd for $\text{C}_{15}\text{H}_{12}\text{N}_2\text{O}_2$: C, 71.42; H, 4.80; N, 11.11. Found: C, 71.31; H, 4.83; N, 11.14.

Ethyl 2-amino-5-(3-methyl-5-isoxazolyl)-6-phenylnicotinate (5af): mp 171.1-172.3°C (from ethyl acetate-hexane); IR(KBr) $\nu_{\max}/\text{cm}^{-1}$ 3415, 3275, 1699 ($\nu_{\text{C=O}}$); ^1H NMR(CDCl_3) δ 1.36 (3H, t, $J = 7.1$ Hz, CH_2CH_3), 2.07(3H, s, Isoxazolyl- CH_3), 4.21(2H, q, $J = 7.1$ Hz, CH_2CH_3), 5.01(1H, s, Isoxazolyl-H), 6.43(2H, br s, NH_2), 7.07(5H, m, Ph-H), 8.21(1H, s, Py-H); MS m/z 323(M^+ , 100%); *Anal.* Calcd for $\text{C}_{18}\text{H}_{17}\text{N}_3\text{O}_3$: C, 66.86; H, 5.30; N, 13.00. Found: C, 66.90; H, 5.35; N, 12.97.

6-Amino-3-(3-methyl-5-isoxazolyl)-2-phenylpyridine (5ag): mp 215.0-215.5°C (from acetone-hexane); IR(KBr) $\nu_{\max}/\text{cm}^{-1}$ 3303, 3180; ^1H NMR (DMSO- d_6): δ 2.11(3H, s, Isoxazolyl- CH_3), 5.20(1H, s, Isoxazolyl-H), 5.55(2H, br s, NH_2), 6.57(1H, d, $J = 8.6$ Hz, Py-H), 7.21(5H, m, Ph-H), 7.68(1H, d, $J = 8.6$ Hz, Py-H); MS m/z 251(M^+ , 24%), 47(100); HRMS: Found: 251.1076. Calcd for $\text{C}_{15}\text{H}_{13}\text{N}_3\text{O}$: 251.1057.

1-(2-Cyanoethenyl) amino-2-(3-methyl-5-isoxazolyl)-1-phenylethene (7ag): mp 145.3-147.3°C (from ethyl acetate-hexane); IR(KBr) $\nu_{\max}/\text{cm}^{-1}$ 3230, 2204($\nu_{\text{C=N}}$), 1641 ($\nu_{\text{C=C}}$); ^1H NMR(CDCl_3) δ 2.22 (3H, s, Isoxazolyl- CH_3), 4.26(1H, d, $J = 13.2$ Hz, =CH), 5.28(1H, s, Isoxazolyl-H), 5.65(1H, s, =CH), 6.68(1H, d, $J = 13.2$ Hz, =CH), 7.17(5H, m, Ph-H), 8.32 (1H, br d, NH); MS m/z 251(M^+ , 100%); HRMS: Found: 251.1042. Calcd for $\text{C}_{15}\text{H}_{13}\text{N}_3\text{O}$: 251.1057.

2-Amino-3-cyano-5-(3-methyl-5-isoxazolyl)-6-phenylpyridine (5ah): mp 187.2-188.1°C (from ethyl acetate-hexane); IR(KBr) $\nu_{\max}/\text{cm}^{-1}$ 3360, 3180, 2230 ($\nu_{\text{C=N}}$); ^1H NMR(CDCl_3) δ 2.07(3H, s, Isoxazolyl- CH_3), 5.10(1H, s, Isoxazolyl-H), 5.33(2H, br s, NH_2), 7.13 (5H, m, Ph-H), 7.83(1H, s, Py-H); MS m/z 276(M^+ , 100%); HRMS Found: 276.1009. Calcd for $\text{C}_{16}\text{H}_{12}\text{N}_4\text{O}$: 276.1009. *Anal.* Calcd for $\text{C}_{16}\text{H}_{12}\text{N}_4\text{O}$: C, 69.55; H, 4.38; N, 20.28. Found: C, 69.34; H, 4.36; N, 19.87.

1-(2,2-Dicyanoethenyl) amino-2-(3-methyl-5-isoxazolyl)-1-phenylethene (7ah): mp 172.9-174.4°C (from ethyl acetate-hexane); IR(KBr) $\nu_{\max}/\text{cm}^{-1}$ 3330, 2218($\nu_{\text{C=N}}$), 1665 ($\nu_{\text{C=C}}$); ^1H NMR(CDCl_3) δ 2.25(3H, s, Isoxazolyl- CH_3), 5.62(1H, s, Isoxazolyl-H), 5.83(1H, s, =CH), 7.22(6H, m, =CH and Ph-H), 9.21(1H, br d, NH); ms m/z 276(M^+ , 100%); HRMS: Found: 276.1011. Calcd for $\text{C}_{16}\text{H}_{12}\text{N}_4\text{O}$: 276.1010.

3-acetyl-2-methyl-6-phenyl-5-(2-pyridyl)pyridine (5ba): mp 98.5-99.4°C (from acetone-hexane); IR(KBr) $\nu_{\max}/\text{cm}^{-1}$ 1680($\nu_{\text{C=O}}$); ^1H NMR(CDCl_3) δ 2.59 (3H, s, Py- CH_3), 2.78(3H, m, COCH_3), 6.69-8.30(4H, ABCD spin system, Py-H), 7.15 (5H, m, Ph-H), 8.13(1H, s, Py-H); MS m/z 288(M^+ , 32%), 278 (100%); *Anal.* Calcd for $\text{C}_{19}\text{H}_{16}\text{N}_2\text{O}$: C, 79.14; H, 5.59; N, 9.72. Found: C, 79.04; H, 5.58; N, 9.43.

Methyl 2-methyl-6-phenyl-5-(2-pyridyl)nicotinate (5bb): mp 80.6-81.4°C (from ether-hexane); IR(KBr) $\nu_{\max}/\text{cm}^{-1}$ 1715($\nu_{\text{C=O}}$); $^1\text{H NMR}(\text{CDCl}_3)$ δ 2.86(3H, s, Py-CH₃), 3.83(3H, s, COOCH₃), 6.66-8.46(4H, ABCD spin system, Py-H), 7.10(5H, m, Ph-H), 8.30(1H, s, Py-H); MS m/z 304(M⁺, 33%), 303(100%); *Anal.* Calcd for C₁₉H₁₆N₂O₂: C, 74.98; H, 5.30; N, 9.21. Found: C, 74.96; H, 5.36; N, 9.18.

3-(2-Pyridyl)-2-phenyl-6-trifluoromethylpyridine (5bc): mp 89.3-90.3°C (from ether-hexane); IR(KBr) $\nu_{\max}/\text{cm}^{-1}$ 1185-1120($\nu_{\text{C-F}}$); $^1\text{H NMR}(\text{CDCl}_3)$ δ 6.59-8.36(4H, ABCD spin system, Py-H), 7.00(5H, m, Ph-H), 7.40(1H, d, $J = 7.7$ Hz, Py-H), 7.83(1H, d, $J = 7.7$ Hz, Py-H); $^{19}\text{F NMR}(\text{CDCl}_3)$ δ -68.4(m, CF₃); MS m/z 300(M⁺, 30%), 299 (100%); *Anal.* Calcd for C₁₇H₁₁N₂F₃: C, 68.00; H, 3.69; N, 9.33. Found: C, 67.95; H, 3.72; N, 9.23.

3-Ethoxycarbonyl-6-phenyl-5-(2-pyridyl)-2-pyridone (6bd): mp 218.5-220.1°C (from MeOH); IR(KBr) $\nu_{\max}/\text{cm}^{-1}$ 3350, 1695[$\nu_{\text{C=O}}$ ester], 1590($\nu_{\text{C=O}}$); $^1\text{H NMR}(\text{DMSO-d}_6)$ δ 1.26(3H, t, $J = 6.6$ Hz, CH₂CH₃), 4.06(2H, q, $J = 6.6$ Hz, CH₂CH₃), 6.33-8.10(4H, ABCD spin system, Py-H), 6.92(5H, m, Ph-H), 7.89(1H, s, Py-H); MS m/z 320(M⁺, 100%); HRMS: Found: 320.1152. Calcd for C₁₉H₁₆N₂O₃: 320.1159.

5-(2-Pyridyl)-6-phenyl-2-pyridone (6be): mp 261.3-263.5°C (from MeOH); IR(KBr) $\nu_{\max}/\text{cm}^{-1}$ 2850, 1640($\nu_{\text{C=O}}$); $^1\text{H NMR}(\text{DMSO-d}_6)$ δ 6.45(1H, d, $J = 8.7$ Hz, Py-H), 6.66-8.48(4H, ABCD spin system, Py-H), 7.15-7.44(5H, m, Ph-H), 7.77(1H, d, $J = 8.7$ Hz, Py-H), 11.71(1H, br s, NH); MS m/z 248(M⁺, 32%), 247(100%); *Anal.* Calcd for C₁₆H₁₂N₂O: C, 77.40; H, 4.87; N, 11.28. Found: C, 77.22; H, 4.80; N, 11.23.

Ethyl 2-amino-6-phenyl-5-(2-pyridyl)nicotinate (5bf): mp 162.6-164.1°C (from ethyl acetate-hexane); IR(KBr) $\nu_{\max}/\text{cm}^{-1}$ 3410, 3250, 1695($\nu_{\text{C=O}}$); $^1\text{H NMR}(\text{CDCl}_3)$ δ 1.31(3H, t, $J = 6.9$ Hz, CH₂CH₃), 4.17(2H, q, $J = 6.9$ Hz, CH₂CH₃), 6.83 (2H, br s, NH₂), 6.42-8.24(4H, ABCD spin system, Py-H), 6.98(5H, m, Ph-H), 8.14(1H, s, Py-H); MS m/z 319 (M⁺, 40%), 318(100%); *Anal.* Calcd for C₁₉H₁₇N₃O₂: C, 71.46; H, 5.37; N, 13.16. Found: C, 71.31; H, 5.22; N, 13.10.

2-Amino-3-cyano-6-phenyl-5-(2-pyridyl)pyridine (5bh): mp 149.7-150.2°C (from CCl₄); IR(KBr) $\nu_{\max}/\text{cm}^{-1}$ 3450, 3270, 2200($\nu_{\text{C=N}}$); $^1\text{H NMR}(\text{CDCl}_3)$ δ 5.46(2H, br s, NH₂), 6.53-8.33(4H, ABCD spin system, Py-H), 7.07(5H, m, Ph-H), 7.83(1H, s, Py-H); MS m/z 272(M⁺, 28%), 271(100%); *Anal.* Calcd for C₁₇H₁₂N₄: C, 74.98; H, 4.44; N, 20.58. Found: C, 74.56; H, 4.41; N, 20.61.

Crystal Data for 5bf: C₁₉H₁₇N₃O₂, F.W. = 319.36, triclinic, space group $P\bar{1}$ (#2), $a = 10.460(3)$, $b = 11.291(4)$, $c = 8.213(2)$ Å, $\alpha = 97.00(3)$, $\beta = 109.90(2)$, $\gamma = 110.16(2)^\circ$, $V = 824.2(5)$ Å³, $Z = 2$, $D_{\text{calc}} = 1.287$ g/cm³, $\mu(\text{MoK}_\alpha) = 0.80$ cm⁻¹, crystal dimensions 0.28 x 0.32 x 0.94 mm. Measurement was made on a Rigaku AFC5S diffractometer with graphite monocromated MoK_α radiation. The data were collected at 24 ± 1°C using the $\omega/2\theta$ scan technique to a maximum 2θ value of 55.0°. Of the 3991 reflections which were

collected, 3784 were unique ($R_{\text{int}} = 0.026$). The structure was solved by direct methods (SIR88).²¹ The non-hydrogen atoms were refined anisotropically and all the hydrogen atoms were refined isotropically. The final cycle of full-matrix least-squares refinement was based on 2026 observed reflections [$I > 3.00 \sigma(I)$] and 286 variable parameters and converged with unweighted and weighted agreement factors of R (0.046) and R_w (0.056). All calculations were performed using the TEXSAN²² crystallographic software package of Molecular Structure Corporation.

Attempt to cyclize 7ah: A 15% solution of *n*-BuLi (0.6 mL, 1.0 mmol) in hexane was added to a solution of diisopropylamine (101.2 mg, 1.0 mmol) in THF (10 mL) at -80°C with stirring under nitrogen atmosphere. After 1 h stirring, 227.3 mg (1.0 mmol) of **7ah** in THF (3 mL) was slowly added to the solution, and the mixture was stirred for an additional 1 h. The mixture was finally refluxed for 14 h after stirring for 2 h at rt. After cooling to -5°C , the resulting mixture was quenched with water (10 mL), and extracted with ether. The organic extracts was dried (Na_2SO_4) and evaporated *in vacuo*. The product was applied to TLC analysis (SiO_2 , ether or CH_2Cl_2), and **7ah** was recovered in the chemically pure form without any by-products.

ACKNOWLEDGEMENT

We are grateful to Ube Industry Co. Ltd. for supplying **4e** and **4g**. The present work was partially supported by Japan Private School Promotion Foundation (1997-1999).

REFERENCES

1. J. K. Whitesell and M. A. Whitesell, *Synthesis*, 1983, 517; for earlier works, see: D. A. Evans, *J. Am. Chem. Soc.*, 1970, **92**, 7593 and G. Wittig, R. Roderer, and S. Fischer, *Tetrahedron Lett.*, 1973, 3517.
2. R. T. Coutts and A. F. Casy, In *Pyridine and Its Derivatives*, Supplement IV; ed. By R. A. Abramovitch, Wiley, New York, 1975; p. 445.
3. T. Konakahara and K. Sato, *Bull. Chem. Soc. Jpn.*, 1983, **56**, 1241.
4. T. Konakahara and Y. Takagi, *Heterocycles*, 1980, **14**, 393.
5. T. Konakahara and Y. Kurosaki, *J. Chem. Res.(S)*, 1989, 130; *J. Chem. Res.(M)*, 1989, 1068.
6. T. Konakahara, M. Hojahmat, and K. Sujimoto, *Heterocycles*, 1997, **45**, 271.
7. T. Konakahara, M. Sato, T. Haruyama, and K. Sato, *Nippon Kagaku Kaishi*, 1990, 466.
8. T. Konakahara, A. Watanabe, and K. Sato, *Heterocycles*, 1985, **23**, 383.
9. T. Konakahara, A. Watanabe, K. Maehara, M. Nagata, and M. Hojahmat, *Heterocycles*, 1993, **35**, 1171.
10. O. Tsuge, K. Masuda, and S. Kanemasa, *Heterocycles*, 1983, **20**, 593.
11. T. Konakahara, M. Hojahmat, and S. Tamura, *J. Chem. Soc., Perkin Trans. 1*, 1999, 2803.
12. T. Konakahara and Y. Takagi, *Synthesis*, 1979, 192.
13. The authors have deposited atomic coordinates for this structure with the Cambridge Crystallographic Data Center. The coordinates can be obtained on request from The Director, Cambridge Crystallographic Data Center, University Chemical Laboratory, Lenfield Road, Cambridge CB2 1EW, U.K.

14. C. K. Johnson, 'ORTEP II, A Fortran Thermal-Ellipsoids Plot Program for Crystal Structure Illustrations,' Report ORLN-5138. Oak Ridge National Laboratory, Oak Ridge, Tennessee, 1976.
15. T. Konakahara, N. Sugama, and K. Sato, *Heterocycles*, 1992, **33**, 157.
16. MO (PM3 method) calculations were accomplished using the computer programs package CAChe Worksystem, supplied from Oxford Molecular Ltd.
17. K. Ito, S. Yokokura, and S. Miyajima, *J. Heterocycl. Chem.*, 1989, **26**, 773.
18. T. Nishimura, H. Misawa, H. Kurihara, and H. Yamanaka, *Jpn. Kokai Tokkyo Koho*, **78**, 69,835 (*Chem. Abstr.* 1979, **90**, 22841k).
19. L. Crombie, D. E. Games, and A. W. G. James, *J. Chem. Soc. Perkin Trans. 1*, 1979, 464.
20. M. Hojo, R. Masuda, Y. Kokuryo, and H. Shioda, *Chem. Lett.*, 1976, 499.
21. M. C. Burla, M. Camalli, G. Cascarano, C. Giacovazzo, G. Polidori, R. Spagna, and D. Viterbo, SIR88. A Direct-Methods Program for the Automatic Solution of Crystal Structures; *J. Appl. Cryst.*, 1989, **22**, 389.
22. TEXSAN-TEXRAY Structure Analysis Package, Molecular Structure Corporation, 1985.