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# 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

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***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.

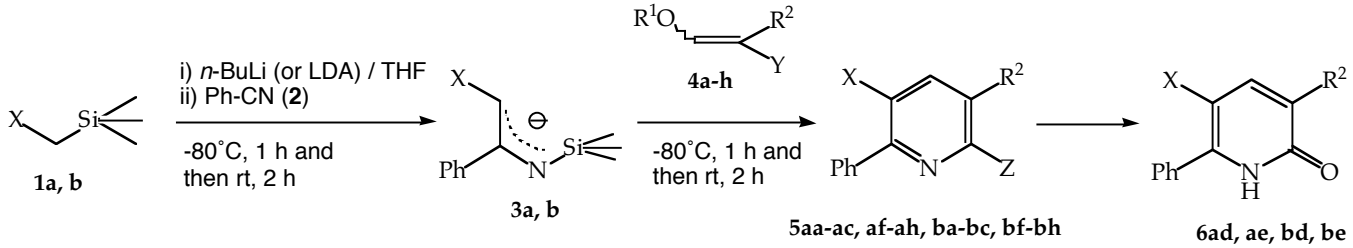
## INTRODUCTION

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 anions[3-5] and 1,3-diphenyl-2-propen-1-one[6] 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 $^1$H NMR in parentheses.

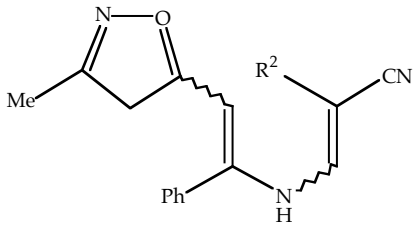
[d] Stirred for 1 h at -80 °C and then for 2 h under reflux in THF.

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

[f] Considerable amount of 2-phenacylpyridine[3] 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 $^1$H 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




**7ag, ah**

trifluoroacetyl groups as substituent Y cyclized more easily to give **5** than the alkoxycarbonyl 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 analysis[13] and the structures of the other products were deduced by a comparison of the spectroscopic data with those of **5bf**. ORTEP[14] 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).

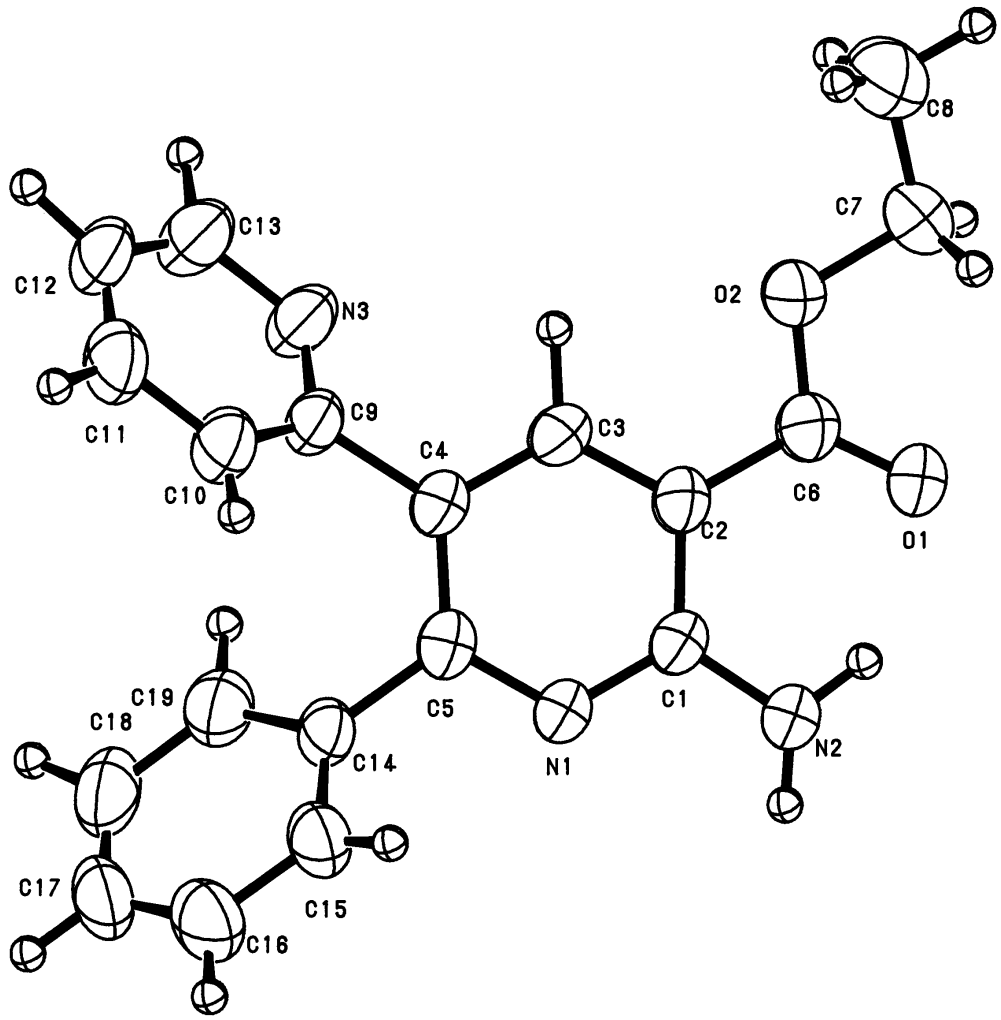



Figure 1. ORTEP[14] drawing of ethyl 2-amino-6-phenyl-5-(2-pyridyl)nicotinate (**5bf**)

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]

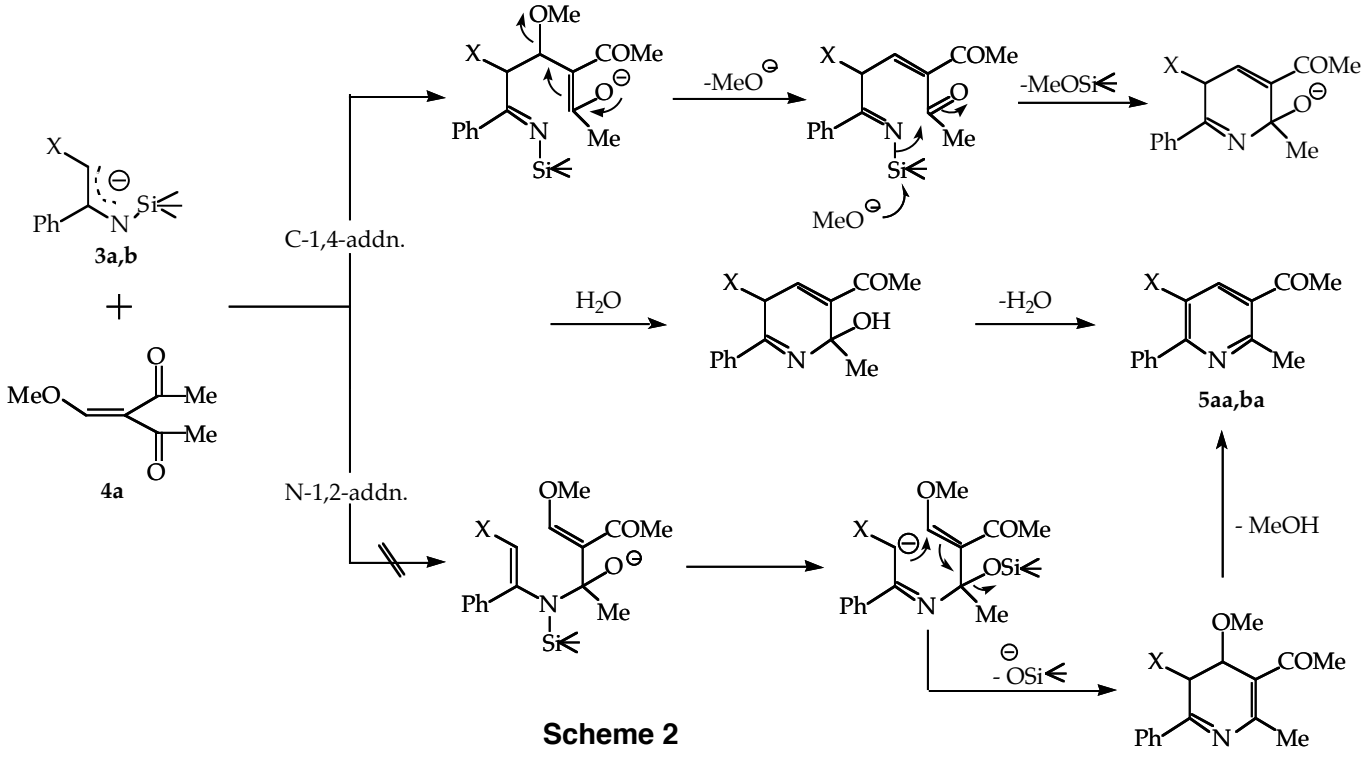
Table 3. Coefficients[a] for LUMO of Michel acceptors (**4a,f,g**)

| **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]




**Scheme 2**

## EXPERIMENTAL

All mps (Yanagimoto micro-melting point apparatus) are uncorrected. IR spectra were taken on a JEOL IR-5300 spectrophotometer. $^1$H NMR spectra were determined with a JNM PMX-60SI, FX-90Q, or AL-300 spectrometer for solutions in $CDCl_3$ or DMSO-$d_6$. Chemical shifts are reported in δ values (internal standard $Me_4Si$). $^{19}$F NMR spectra were determined with a JNM FX-90Q spectrometer for solutions in $CDCl_3$, and chemical shifts are also reported in δ values (negative for upper-field than an internal standard, $CFCl_3$). 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-trimethylsilylmethylisoxazole[5] (**1a**), 2-(trimethylsilylmethyl)pyridine[3] (**1b**), 3-acetyl-4-methoxy-3-buten-2-one[10] (**4a**), methyl 2-acetyl-3-methoxy-2-propenoate[19] (**4b**) and 1,1,1-

trifluoro-4-ethoxy-3-buten-2-one[20] (**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 $NH_4Cl$ solution (50 mL) at 0°C, and extracted with ether. The organic extracts were dried ($Na_2SO_4$) and evaporated *in vacuo*. The crude product was recrystallized from acetone-hexane (or chromatographed on silica gels eluting with $CHCl_3$, $CH_2Cl_2$, 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) $\nu_{max}$/cm$^{-1}$ 1695($\nu_{C=O}$); $^1$H NMR ($CDCl_3$) δ 2.10(3H, s, Isoxazolyl-$CH_3$), 2.56(3H, s, Py-$CH_3$), 2.71(3H, s, $COCH_3$), 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 $C_{18}H_{17}N_3O_2$: 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) $\nu_{max}$/cm$^{-1}$ 1730($\nu_{C=O}$); $^1$H NMR($CDCl_3$) δ 2.10(3H, s, Isoxazolyl-$CH_3$), 2.79 (3H, s, Py-$CH_3$), 3.79(3H, s, $COOCH_3$), 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 $C_{18}H_{17}N_3O_3$: 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) $\nu_{max}$/cm$^{-1}$ 1190-1105($\nu_{C-F}$); $^1$H NMR($CDCl_3$) δ 2.10(3H, s, Isoxazolyl-$CH_3$), 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); $^{19}$F NMR($CDCl_3$) δ -68.6(m, $CF_3$); MS *m/z* 304 ($M^+$, 83%), 263(100%); *Anal.* Calcd for $C_{16}H_{11}N_2OF_3$: 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) $\nu_{max}$/cm$^{-1}$ 2910, 1740[$\nu_{C=O}$ (ester)], 1648($\nu_{C=O}$); $^1$H NMR(DMSO-$d_6$) δ 1.26(3H, t, *J* = 7.1 Hz, $CH_2CH_3$), 2.02(3H, s, Isoxazolyl-$CH_3$), 4.14(2H, q, *J* = 7.1 Hz, $CH_2CH_3$), 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 $C_{18}H_{16}N_2O_4$: 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) $\nu_{max}/cm^{-1}$ 2920, 1648($\nu_{C=O}$); $^1H$ 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 $C_{15}H_{12}N_2O_2$: 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) $\nu_{max}/cm^{-1}$ 3415, 3275, 1699 ($\nu_{C=O}$); $^1H$ NMR($CDCl_3$) δ 1.36 (3H, t, *J* = 7.1Hz, $CH_2C\underline{H}_3$), 2.07(3H, s, Isoxazolyl-$CH_3$), 4.21(2H, q, *J* = 7.1Hz, $C\underline{H}_2CH_3$), 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 $C_{18}H_{17}N_3O_3$: 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) $\nu_{max}/cm^{-1}$ 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 $C_{15}H_{13}N_3O$: 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) $\nu_{max}/cm^{-1}$ 3230, 2204($\nu_{C\equiv N}$), 1641 ($\nu_{C=C}$); $^1H$ 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 $C_{15}H_{13}N_3O$: 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) $\nu_{max}/cm^{-1}$ 3360, 3180, 2230 ($\nu_{C\equiv N}$); $^1H$ 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 $C_{16}H_{12}N_4O$: 276.1009. *Anal.* Calcd for $C_{16}H_{12}N_4O$: 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) $\nu_{max}/cm^{-1}$ 3330, 2218($\nu_{C\equiv N}$), 1665 ($\nu_{C=C}$); $^1H$ 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 $C_{16}H_{12}N_4O$: 276.1010.

**3-acetyl-2-methyl-6-phenyl-5-(2-pyridyl)pyridine (5ba)**: mp 98.5-99.4°C (from acetone-hexane); IR(KBr) $\nu_{max}/cm^{-1}$ 1680($\nu_{C=O}$); $^1H$ 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 $C_{19}H_{16}N_2O$: 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) $\nu_{max}/cm^{-1}$ 1715($\nu_{C=O}$); $^1H$ NMR($CDCl_3$) δ 2.86(3H, s, Py-$CH_3$), 3.83(3H, s, $COOCH_3$), 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 $C_{19}H_{16}N_2O_2$: 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) $\nu_{max}/cm^{-1}$ 1185-1120($\nu_{C-F}$); $^1H$ NMR ($CDCl_3$) 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); $^{19}F$ NMR($CDCl_3$) δ -68.4(m, $CF_3$); MS *m/z* 300($M^+$, 30%), 299 (100%); *Anal.* Calcd for $C_{17}H_{11}N_2F_3$: 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) $\nu_{max}/cm^{-1}$ 3350, 1695[($\nu_{C=O}$) ester], 1590($\nu_{C=O}$); $^1H$ NMR (DMSO-$d_6$) δ 1.26(3H, t, *J* = 6.6 Hz, $CH_2CH_3$), 4.06(2H, q, *J* = 6.6 Hz, $CH_2CH_3$), 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 $C_{19}H_{16}N_2O_3$: 320.1159.

**5-(2-Pyridyl)-6-phenyl-2-pyridone (6be)**: mp 261.3-263.5°C (from MeOH); IR(KBr) $\nu_{max}/cm^{-1}$ 2850, 1640($\nu_{C=O}$); $^1H$ NMR (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 $C_{16}H_{12}N_2O$: 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) $\nu_{max}/cm^{-1}$ 3410, 3250, 1695($\nu_{C=O}$); $^1H$ NMR($CDCl_3$) δ 1.31(3H, t, *J* = 6.9 Hz, $CH_2CH_3$), 4.17(2H, q, *J* = 6.9 Hz, $CH_2CH_3$), 6.83 (2H, br s, $NH_2$), 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 $C_{19}H_{17}N_3O_2$: 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 $CCl_4$); IR(KBr) $\nu_{max}/cm^{-1}$ 3450, 3270, 2200($\nu_{C\equiv N}$); $^1H$ NMR ($CDCl_3$) δ 5.46(2H, br s, $NH_2$), 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 $C_{17}H_{12}N_4$: C, 74.98; H, 4.44; N, 20.58. Found: C, 74.56; H, 4.41; N, 20.61.

**Crystal Data for 5bf:** $C_{19}H_{17}N_3O_2$, F.W. = 319.36, triclinic, space group $P\bar{1}$ (#2), *a* = 10.460(3), *b* = 11.291(4), *c* = 8.213(2) Å, α = 97.00(3), β = 109.90(2), γ = 110.16(2)°, *V* = 824.2(5) $Å^3$, *Z* = 2, $D_{calc}$ = 1.287 $g/cm^3$, μ($MoK_\alpha$) = 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 $MoK_\alpha$ radiation. The data were collected at 24 ± 1°C using the ω/2θ scan technique to a maximum 2θ value of 55.0°. Of the 3991 reflections which were

collected, 3784 were unique ($R_{int}$ = 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 TEXSAN[22] 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.

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