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,† most of them have been utilized for the carbon-carbon bond formation. Utility of anions bearing a trialkysilyl 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.‡ 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§–‖ and 1,3-diphenyl-2-propen-1-one* or perfluoro(2-methyl-2-pentene).¶ 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.¶–‖ 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,‡ 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.§,¶ 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-
icotinate (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)

<table>
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<th>Xb</th>
<th>4</th>
<th>R1</th>
<th>R2</th>
<th>Y</th>
<th>Product</th>
<th>Z</th>
<th>Yield of 5 or 6 (%)c</th>
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<tr>
<td>a</td>
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<td>COMe</td>
<td>COMe</td>
<td>5aa</td>
<td>Me</td>
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<td>Me</td>
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<td>Et</td>
<td>H</td>
<td>COCF3</td>
<td>5ac</td>
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<td>Me</td>
<td>H</td>
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<td>CN</td>
<td>CN</td>
<td>5bh</td>
<td>NH2</td>
<td>25[nd]eg</td>
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</table>

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 R² 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

![Diagram](https://via.placeholder.com/150)

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 R² 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 and the structures of the other products were deduced by a comparison of the spectroscopic data with those of 5bf. ORTEP 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, 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.

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, 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\textsuperscript{14} drawing of ethyl 2-amino-6-phenyl-5-(2-pyridyl)nicotinate (5bf)

Table 2. Coefficients\textsuperscript{a} for HOMO of N-silyl-1-azaallyl anions (3a,b)

<table>
<thead>
<tr>
<th>3</th>
<th>HOMO coefficients</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>N1: 0.249, C3: -0.623</td>
</tr>
<tr>
<td>b</td>
<td>N1: -0.459, C3: 0.637</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Calculated by PM3 method.\textsuperscript{16}

Table 3. Coefficients\textsuperscript{a} for LUMO of Michel acceptors (4a,f,g)

<table>
<thead>
<tr>
<th>4</th>
<th>LUMO coefficients</th>
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<tr>
<td>a</td>
<td>C2\textsuperscript{b} (COR): 0.050, C2\textsuperscript{b} (CN): --, C4: 0.659</td>
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<tr>
<td>f</td>
<td>C2\textsuperscript{b} (COR): 0.288, C2\textsuperscript{b} (CN): 0.146, C4: -0.702</td>
</tr>
<tr>
<td>g</td>
<td>C2\textsuperscript{b} (COR): --, C2\textsuperscript{b} (CN): -0.282, C4: 0.680</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Calculated by PM3 method.\textsuperscript{16}  \textsuperscript{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.\textsuperscript{17, 18}

Further mechanistic investigation is in progress. Miyajima and his co-workers have reported the synthesis of pyridine derivatives from \textit{N}-\textit{t}-butyliminines and 4d, 4f, or 4h at an elevated temperature.\textsuperscript{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.\textsuperscript{18}

\begin{itemize}
  \item \textbf{EXPERIMENTAL}
\end{itemize}

All mps (Yanagimoto micro-melting point apparatus) are uncorrected. IR spectra were taken on a JEOL IR-5300 spectrophotometer. \textsuperscript{1}H NMR spectra were determined with a JNM PMX-60SI, FX-90Q, or AL-300 spectrometer for solutions in CDCl\textsubscript{3} or DMSO-d\textsubscript{6}. Chemical shifts are reported in \( \delta \) values (internal standard Me, Si). \textsuperscript{19}F NMR spectra were determined with a JNM FX-90Q spectrometer for solutions in CDCl\textsubscript{3}, and chemical shifts are also reported in \( \delta \) values (negative for upper-field than an internal standard, CFCl\textsubscript{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.

\textbf{Materials:} 3-Methyl-5-trimethylsilylmethylisoxazole\textsuperscript{5} (1a), 2-(trimethylsilylmethyl)pyridine\textsuperscript{3} (1b), 3-acetyl-4-methoxy-3-buten-2-one\textsuperscript{10} (4a), methyl 2-acetyl-3-methoxy-2-propenoate\textsuperscript{19} (4b) and 1,1,1-
trifluoro-4-ethoxy-3-buten-2-one\textsuperscript{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-trimethylsilylmethyloisoxazole (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-acetyl-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\textsubscript{4}Cl solution (50 mL) at 0°C, and extracted with ether. The organic extracts were dried (Na\textsubscript{2}SO\textsubscript{4}) and evaporated in vacuo. The crude product was recrystallized from acetone-hexane (or chromatographed on silica gels eluting with CHCl\textsubscript{3}, CH\textsubscript{2}Cl\textsubscript{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) ν\textsubscript{max}/cm\textsuperscript{-1} 1695(ν\textsubscript{C=O}); \textsuperscript{1}H NMR (CDCl\textsubscript{3}) δ 2.10(3H, s, Isoxazolyl-CH\textsubscript{3}), 2.56(3H, s, Py-CH\textsubscript{3}), 2.71(3H, s, COCH\textsubscript{3}), 5.21(1H, s, Isoxazolyl-H), 7.12(5H, m, Ph-H), 8.07 (1H, s, Py-H); MS m/z 292(M\textsuperscript{+}, 100%); Anal. Calcd for C\textsubscript{18}H\textsubscript{17}N\textsubscript{3}O\textsubscript{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) ν\textsubscript{max}/cm\textsuperscript{-1} 1730(ν\textsubscript{C=O}); \textsuperscript{1}H NMR(CDC\textsubscript{3}) δ 2.10(3H, s, Isoxazolyl-CH\textsubscript{3}), 2.79 (3H, s, Py-CH\textsubscript{3}), 3.79(3H, s, COOCH\textsubscript{3}), 5.27(1H, s, Isoxazolyl-H), 7.14(5H, m, Ph-H), 8.31(1H, s, Py-H); MS m/z 267(M\textsuperscript{+}, 100%); Anal. Calcd for C\textsubscript{18}H\textsubscript{17}N\textsubscript{3}O\textsubscript{2}: 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) ν\textsubscript{max}/cm\textsuperscript{-1} 1190-1105(ν\textsubscript{C=O}); \textsuperscript{1}H NMR(CDC\textsubscript{3}) δ 2.10(3H, s, Isoxazolyl-CH\textsubscript{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); \textsuperscript{19}F NMR(CDC\textsubscript{3}) δ -68.6(m, CF\textsubscript{3}) MS m/z 304 (M\textsuperscript{+}, 83%), 263(100%); Anal. Calcd for C\textsubscript{16}H\textsubscript{11}N\textsubscript{2}F\textsubscript{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) ν\textsubscript{max}/cm\textsuperscript{-1} 2910, 1740(ν\textsubscript{C=O} (ester)], 1648(ν\textsubscript{C=O}); \textsuperscript{1}H NMR(DMSO-d\textsubscript{6}) δ 1.26(3H, t, J = 7.1 Hz, CH\textsubscript{3}CH\textsubscript{2}CH\textsubscript{3}), 2.02(3H, s, Isoxazolyl-CH\textsubscript{3}), 4.14(2H, q, J = 7.1 Hz, CH\textsubscript{2}CH\textsubscript{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\textsuperscript{+}, 100%); Anal. Calcd for C\textsubscript{18}H\textsubscript{16}N\textsubscript{2}O\textsubscript{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) ν max/cm⁻¹ 2920, 1648(ν C=O); ¹H NMR(DMSO-d₆) δ 2.13(3H, s, Isoxazolyl-CH₃), 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 C₁₅H₁₂N₂O₂: 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) ν max/cm⁻¹ 3415, 3275, 1699 (ν C=O); ¹H NMR(CDCl₃) δ 1.36 (3H, t, J = 7.1Hz, CH₂CH₃), 2.07(3H, s, Isoxazolyl-CH₃), 4.21(2H, q, J = 7.1Hz, CH₂CH₃), 5.01(1H, s, Isoxazolyl-H), 6.43(2H, br s, NH₂), 7.07(5H, m, Ph-H), 8.21(1H, s, Py-H); MS m/z 323(M⁺, 100%); Anal. Calcd for C₁₈H₁₇N₃O₃: 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) ν max/cm⁻¹ 3303, 3180; ¹H NMR(DMSO-d₆): δ 2.11(3H, s, Isoxazolyl-CH₃), 5.20(1H, s, Isoxazolyl-H), 5.55(2H, br s, NH₂), 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 C₁₅H₁₃N₃O: 251.1057.

1-(2-Cyanoethyl)amino-2-(3-methyl-5-isoxazolyl)-1-phenylethene (7ag): mp 145.3-147.3°C (from ethyl acetate-hexane); IR(KBr) ν max/cm⁻¹ 3230, 2204(ν C=N), 1641 (ν C=O); ¹H NMR(CDCl₃) δ 2.22 (3H, s, Isoxazolyl-CH₃), 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 C₁₅H₁₃N₃O: 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) ν max/cm⁻¹ 3360, 3180, 2230 (ν C=N); ¹H NMR(CDCl₃) δ 2.07(3H, s, Isoxazolyl-CH₃), 5.10(1H, s, Isoxazolyl-H), 5.33(2H, br s, NH₂), 7.13 (5H, m, Ph-H), 7.83(1H, s, Py-H); MS m/z 276(M⁺, 100%); HRMS Found: 276.1009. Calcd for C₁₆H₁₂N₄O: 276.1009. Anal. Calcd for C₁₆H₁₂N₄O: 276.1014. Found: C, 69.34; H, 4.36; N, 19.87.

1-(2,2-Dicyanoethyl)amino-2-(3-methyl-5-isoxazolyl)-1-phenylethene (7ah): mp 172.9-174.4°C (from ethyl acetate-hexane); IR(KBr) ν max/cm⁻¹ 3330, 2218(ν C=N), 1665 (ν C=O); ¹H NMR(CDCl₃) δ 2.25(3H, s, Isoxazolyl-CH₃), 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 C₁₆H₁₂N₄O: 276.1010.

3-acetyl-2-methyl-6-phenyl-5-(2-pyridyl)pyridine (5ba): mp 98.5-99.4°C (from acetone-hexane); IR(KBr) ν max/cm⁻¹ 1680(ν C=O); ¹H NMR(CDCl₃) δ 2.59 (3H, s, Py-CH₃), 2.78(3H, m, COCH₃), 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⁺, 100%); Anal. Calcd for C₁₉H₁₆N₂O: 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) \( v_{\text{max}}/\text{cm}^{-1} \) 1715(\( \nu_{\text{C=O}} \)); \(^1\)H NMR(\( \text{CDCl}_3 \)) \( \delta \) 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\(_2\)O\(_2\): 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) \( v_{\text{max}}/\text{cm}^{-1} \) 1185-1120(\( \nu_{\text{C=O}} \)); \(^1\)H NMR (\( \text{CDCl}_3 \)) \( \delta \) 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(\( \text{CDCl}_3 \)) \( \delta \) -68.4(m, CF\(_3\)); MS \( m/z \) 300(M*, 30%), 299 (100%); Anal. Calcd for C\(_{17}\)H\(_{11}\)F\(_3\): 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) \( v_{\text{max}}/\text{cm}^{-1} \) 3350, 1695[(\( \nu_{\text{C=O}} \) ester)], 1590(\( \nu_{\text{C=O}} \)); \(^1\)H NMR (\( \text{DMSO-d}_6 \)) \( \delta \) 1.26(3H, t, \( J = 6.6 \) Hz, CH\(_2\)CH\(_3\)), 4.06(2H, q, \( J = 6.6 \) Hz, CH\(_2\)CH\(_3\)), 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\(_{16}\)H\(_{15}\)N\(_2\)O\(_3\): 320.1159.

5-(2-Pyridyl)-6-phenyl-2-pyridone (6be): mp 261.3-263.5°C (from MeOH); IR(KBr) \( v_{\text{max}}/\text{cm}^{-1} \) 2850, 1640(\( \nu_{\text{C=O}} \)); \(^1\)H NMR (\( \text{DMSO-d}_6 \)) \( \delta \) 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\(_2\): C, 77.40; H, 4.87; N, 11.28. Found: C, 77.22; H, 4.80; N, 11.23.

Ethyl 2-aminono-6-phenyl-5-(2-pyridyl)nicotinate (5bf): mp 162.6-164.1°C (from ethyl acetate-hexane); IR(KBr) \( v_{\text{max}}/\text{cm}^{-1} \) 3410, 3250, 1695(\( \nu_{\text{C=O}} \)); \(^1\)H NMR (\( \text{CDCl}_3 \)) \( \delta \) 1.31(3H, t, \( J = 6.9 \) Hz, CH\(_2\)CH\(_3\)), 4.17(2H, q, \( J = 6.9 \) Hz, CH\(_2\)CH\(_3\)), 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\(_{17}\)H\(_{17}\)N\(_3\)O\(_2\): 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) \( v_{\text{max}}/\text{cm}^{-1} \) 3450, 3270, 2200(\( \nu_{\text{C=O}} \)); \(^1\)H NMR (\( \text{CDCl}_3 \)) \( \delta \) 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\(_{16}\)N\(_2\)O\(_2\), F.W. = 319.36, triclinic, space group \( P\overline{1} \) (#2), \( a = 10.460(3) \), \( b = 11.291(4) \), \( c = 8.213(2) \), \( \alpha = 97.00(3) \), \( \beta = 109.90(2) \), \( \gamma = 110.16(2) \), \( V = 824.2(5) \), \( \lambda = 3 \), \( Z = 2 \), \( D_{\text{calc}} = 1.287 \text{ g/cm}^3, \mu(\text{MoK}α) = 0.80 \text{ cm}^{-1} \), crystal dimensions 0.28 x 0.32 x 0.94 mm. Measurement was made on a Rigaku AFC5S diffractometer with graphite monochromated MoK\(_{\alpha}\) radiation. The data were collected at 24 ± 1°C using the \( \omega/2\theta \) scan technique to a maximum \( 2\theta \) 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). 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 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$_2$SO$_4$) and evaporated in vacuo. The product was applied to TLC analysis (SiO$_2$, ether or CH$_2$Cl$_2$), and 7ah was recovered in the chemically pure form without any by-products.

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**REFERENCES**

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.
16. MO (PM3 method) calculations were accomplished using the computer programs package CAChe Worksystem, supplied from Oxford Molecular Ltd.