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A NOVEL SYNTHESIS OF 3-NITROPYRIDINE DERIVATIVES FROM *N*-SILYL-1-AZAALLYL ANIONS

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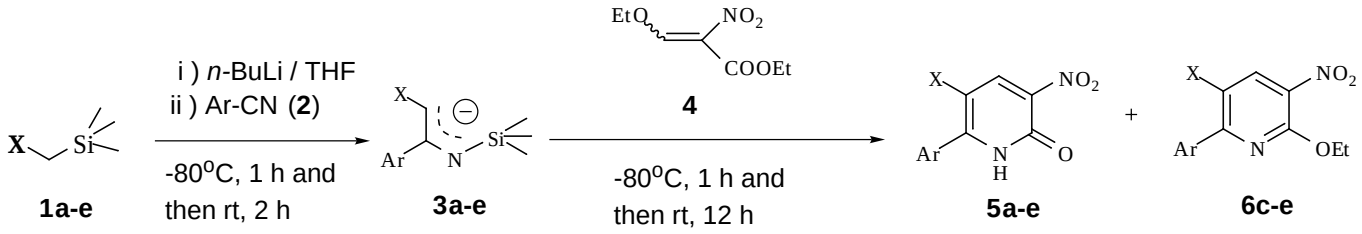
Abstract- Seven kinds of 3-nitropyridines were synthesized from *N*-silyl-1-aza-allyl anions and ethyl 3-etoxy-2-nitropropenoate in good yields, and regio-selectivity of the cyclization was also discussed.

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 derivatives are major components of a variety of natural products and drugs.[2] Although nitropyridines are useful intermediates for medicinals[3, 4] and dyes,[5] the synthetic method is limited because of electron deficiency of the pyridine ring. Recently we have developed an efficient method for the synthesis of 2,3,6-tri-, 2,3,5,6-tetra-, 2,3,4,6-tetra- or 2,3,4,5,6-pentasubstituted pyridine derivatives by the reaction of *N*-silyl-1-azaallyl anions[6-8] with 1,3-diphenyl-2-propen-1-one,[9] several kinds of Michael acceptors such as 3-acethyl-4-methoxy-3-buten-2-one,[10] or perfluoro(2-methyl-2-pentene).[11] 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.[9-15]

As an extension of our study on the synthesis of *N*-heterocyclic compounds, we wish to report a new method to synthesize 3-nitro-2-pyridones (**5**) and/or 3-nitropyridines (**6**) by a one-pot [3+3] cyclization reaction of *N*-silyl-1-azaallyl anion (**3)** with ethyl 3-ethoxy-2-nitropropenoate (**4**) in this paper

(Shceme1).



Scheme 1

RESULTS AND DISCUSSION

α-Silylcarbanions, derived from the α-functionalized alkylsilanes (**1a-e**) in the presence of butyllithium (*n*-BuLi) or LDA,[16] reacted with benzonitrile (**2a**) or 2-cyanopyridine (**2b**) at -80°C in tetrahydrofuran (THF) to give the corresponding *N*-trimethylsilyl-1-azaallyl anions (**3a-e**) in good yield.[3, 4] The *N*-silyl-1-azaallyl anions (**3a-e**) were treated with ethyl 3-ethoxy-2-nitropropenoate (**4**) (a mixture of *E* / *Z*-isomers) for 1 h at -80°C, and then for 12 h at room temperature to give the pyridine derivatives (**5a-d**) or (**6c-e**) as shown in Scheme 1 and Table 1. For example, the reaction of 2-phenyl-3-(2-pyridyl)-*N*-silyl-1-azaallyl anion (**3a**) with **4** selectively gave 3-nitro-6-phenyl-5-(2-pyridyl)-2-pyridone (**5a**) in 95% yield. Furthermore, 2-phenyl-*N*-silyl-3-(2-thiazolinyl)-1-azaallyl anion (**3b**) gave also the corresponding 2-pyridone derivative (**5b**) as a single product in high yield. 3-(3-Methyl-5-isoxazolyl)-2-phenyl-*N*-silyl-1-azaallyl anion (**3c**), however, gave 2-ethoxy-5-(3-methyl-5-isoxazolyl)-3-nitro-6-phenylpyridine (**6c**) as a major product, accompanied with a small amount of 5-(3-methyl-5-isoxazolyl)-3-nitro-6-phenyl-2-pyridone (**5c**). On the other hand, there was no selectivity in the reaction of *N*-silyl-1-azaallyl anion (**3d**).

Table 1. Synthesis of 3-nitro-2-pyridones (**5a-e**) and 3-nitropyridines (**6c-e**)[a]

1	X[b]	**2**	Ar	**3**, **5**, **6**	Yield[c] of **3** (%)	Yield[d] (%) of products	
						5	**6**
a	2-Py	**a**	Ph	**a**	100	95 (95)	
b	2-TAZ	**a**	Ph	**b**	74	67 (90)	
c	5-MIX	**a**	Ph	**c**	74	15 (20)	59 (80)
d	DMC	**a**	Ph	**d**	100	30 (30)	39 (39)
e	TBOC	**b**	2-Py	**e**	68	nd[e]	33 (49)

[a] Molar ratio, **1** : *n*-BuLi : **2** : **4** = 1 : 1 : 1 : 1; stirred for 1 h at -80°C and then 12 h (or 2 h for the reaction of **3a**) at room temperature in THF; LDA was used in the reaction of **1a** instead of *n*-BuLi.

[b] 2-TAZ: 2-thiazolinyl, 5-MIX: 5-(3-methyl)isoxazolyl, DMC: *N*,*N*-dimethylcarbamoyl, TBOC: *t*-butoxycarbonyl

[c] Yield of the corresponding ketone, obtained quantitatively after acidic hydrolysis.

[d] Yield based on the generated **3** in parentheses.

[e] nd: Not determined

The summed yield of the pyridines (**5**) and (**6**) is higher than 90% except for **3d,e**. Furthermore, the C-1,4 adduct was the sole product in the present reaction; that is to say, no N-1,4 adduct was observed. The reaction mechanism will be discussed below.

The structure of **6e** was confirmed by a single crystal X-Ray structural analysis[17] and the structures of the other products (**6c,d**) were deduced by a comparison of the spectroscopic data with those of **6e**. ORTEP[18] drawing is shown in Figure 1. The structures of **5a-d** were determined by their spectroscopic properties (see EXPERIMENTAL). For example, IR spectrum of **5c** showed the absorption band for the 2-pyridone skeleton at 1675 cm^{-1}, which is nearly equal to that of 3-ethoxycarbonyl-5-(3-methyl-5-isoxazolyl)-6-phenyl-2-pyridone.[7] ^1H NMR spectrum showed a singlet at δ 8.86 for the proton on C4 atom of the

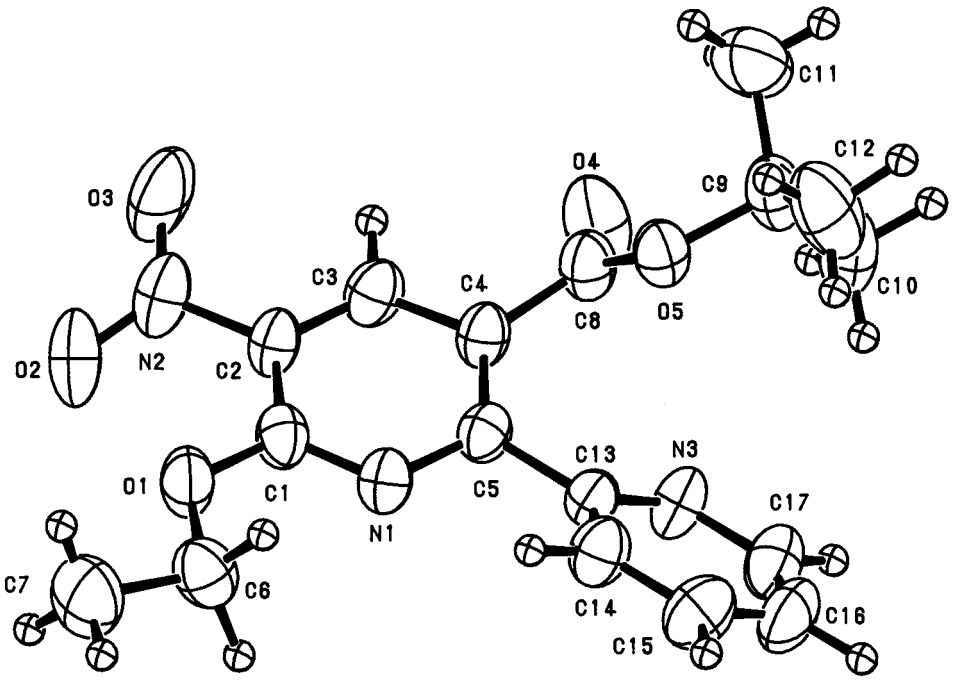


Figure 1. ORTEP[18] drawing of *t*-butyl 6-ethoxy-5-nitro-2-(2-pyridyl)nicotinate (**6e**)

pyridine ring and a broad singlet at δ 11.43 for the imide proton.

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-e** and **4** were calculated by PM3 method,[19] and are shown in Tables 2 and 3 with their HOMO or LUMO energies. In all *N*-silyl-1-azaallyl anions **3a-e**, the HOMO coefficients of the C3 atoms (Scheme 2) are larger than those of the N1 atoms; and the LUMO coefficient (-0.7154 for *E*-4 or -0.7274 for *Z*-4) of the C4 atom (Scheme 2) of **4** is larger than that of the C2 atom (0.0395 or 0.3006). Therefore, bond formation between the C3 atom of **3** and the C4 atom of **4** (the C-1,4-addition) is preferred to the alternative N-1,2-addition in the formation of **5** (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.

Table 2. Orbital energy and coefficients[a] for HOMO of *N*-silyl-1-azaallyl anions (**3a-e**)

3	HOMO energy (eV)	HOMO coefficients N1[b]	HOMO coefficients C3[b]
a	-3.0204	0.3782	- 0.5376
b	-3.2566	- 0.3841	0.5371
c	-3.1803	- 0.3448	0.5043
d	-3.3785	0.4668	- 0.5871
e	-3.3753	- 0.4493	0.5498

[a] Calculated by PM3 method.[16]

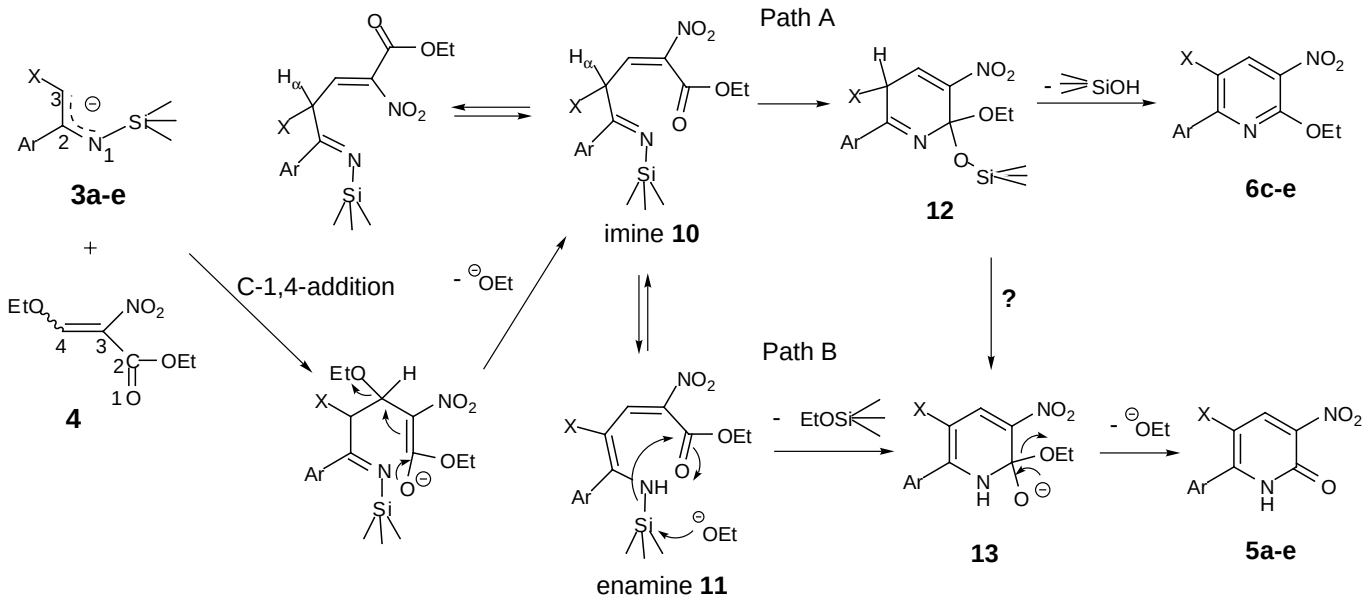
[b] N1 and C3 denote the nitrogen and carbon atoms of *N*-silyl-1-azaally anions (**3a-e**)

Table 3. Orbital energy and coefficients[a] for LUMO of ethyl 3-ethoxy-2-nitropropenoate (**4**)

4	LUMO energy (eV)	LUMO coefficients C2[b]	LUMO coefficients C4[b]
E	-0.9884	0.0395	-0.7154
Z	-0.9043	0.3006	-0.7274

[a] Calculated by PM3 method.[16]

[b] C2 and C4 denote the ethoxycarbonyl and ethoxymethylene carbons of **4**, respectively.



Scheme 2

The modified[7] and plausible reaction mechanism is shown in Scheme 2. After bond formation between

the C3 atom of **3** and the C4 atom of **4** (C-1,4-addition), an ethoxide anion is eliminated to afford the corresponding imine (**10**). 2-Py and 2-TAZ groups are preferable as substituent X in the formation of **5** and 5-MIX group is a little better in the formation of **6**. If the 2-pyridone (**5**) is formed from the tautomeric enamine (**11**), the selectivity in this reaction should be predictable from the difference in stability between these tautomers (**10**) and (**11**). In spite of our efforts, **10** and **11** were unable to be observed in the reaction mixture, because the succeeding cyclization step should be faster than the addition step. Therefore, heat of formation of **10** and **11** were calculated by PM3 method,[16] and shown in Table 4. Difference in heat of formation $\Delta\Delta H_f$ between **11a** and **10a** (-7.88 kcal/mol) or $\Delta\Delta H_f$ between **11b** and **10b** (-10.34 kcal/mol) is more negative than $\Delta\Delta H_f$ between **11c** and **10c** (-5.41 kcal/mol). Furthermore, net atomic charge Q_α of the α-hydrogen of **10a** (+0.1243) and **10b** (+0.1260) are more positive than that of **10c** (+0.1185). In the case of **11d,e**, $\Delta\Delta H_f$ values are also less negative than that of **11a**, and Q_α values are less positive than that of **10a**. However, it is impossible to discuss the relation between these calculation results and the selectivity, because the summed yields of the products (**5d,e**) and (**6d,e**) were low (69 and 33%, respectively). Another plausible path (**12** → **13** → **5**) to form **5** may be difficult to explain the selectivity of the reaction, but it is unable to exclude the path completely from the mechanism in this work.

Table 4. Heat of formation ΔH_f of **10a,c** and **11a,c** and net atomic charge[a] Q_α of the α-hydrogen in **10a,c**

Compound	ΔH_f / kcal·mol^{-1}	$\Delta\Delta H_{f\,(11\,-\,10)}$ / kcal·mol^{-1}	Q_α
10a	-57.18	-7.88	+0.1243
11a	-65.07		-
10b	-58.96	-10.34	+0.1260
11b	-69.30		-
10c	-60.55	-5.41	+0.1185
11c	-65.96		-
10d	-132.98	-3.07	+0.1109
11d	-136.05		-
10e	-188.01	-4.08	+0.1181
11e	-192.09		-

[a] Calculated by PM3 method.[16]

Recently, it has been reported that the reaction of *primary* enamines with α,β–unsaturated trifluoromethyl ketones gave 2-trifluoromethylpyridines in good yields.[20] Their method, however, requires additional dehydration of the intermediate, followed by oxidation. In comparison with their method, the present

method has the advantages of omission of both additional dehydration and oxidation agents. In our reaction, aromatization of the intermediate is achieved by successive elimination of both the ethoxide anion and silanol (or siloxane and the ethoxide anion). On the other hand, many researchers have reported nitration of pyridines by dinitrogen pentoxide.[21] Although the yield of 3-nitropyridine was high, the yields of the substituted 3-nitropyridine derivatives were not always good. In comparison with their method, the present method also has the advantages the easy handling of the reagents, the higher conversion of the reactants, and the higher yields of the substituted 3-nitropyridine derivatives.

EXPERIMENTAL

All mps (Yanagimoto micro-melting point apparatus) and bps are uncorrected. ^{1}H NMR spectra were determined with a JNM PMX-60SI, Al-300, or EX-400 spectrometer for solutions in $CDCl_3$, CCl_4, or acetone-d_6. Chemical shifts are reported in δ values (internal standard Me_4Si). IR spectra were taken on a JEOL JIR-5300 spectrophotometer. Low and high resolution MS were recorded with a JMS-700 double focusing mass spectrometer at EI (70 eV) mode, unless otherwise indicated as FAB (Xe). Elemental analyses were performed at the Research Center for Advanced Materials in Science University of Tokyo.

Materials: 2-(Trimethylsilylmethyl)pyridine[5] (**1a**), 3-methyl-5-(trimethylsilylmethyl)isoxazole[5] (**1c**), *t*-butyl trimethylsilylacetate[5] (**1d**), *N*,*N*-dimethyl(trimethylsilyl)actamide[22] (**1e**) and ethyl 3-ethoxy-2-nitro-propenoate[23,24] (**4**) were prepared by the methods reported previously. All other reagents were obtained from commercial source.

2-(Trimethylsilyl)methyl-2-thiazoline (1b): 2-Methyl-2-thiazoline (8.55 g, 0.080 mol) was lithiated with *n*-BuLi (a 15 % solution in hexane, 40.94 g, 0.080 mol) in THF at -80°C for 1 h. The mixture was treated with trimethylchlorosilane (9.73 g, 0.080 mol) for 1 h at -80°C, and allowed to warm to rt with stirring during overnight. The resulting mixture was finally quenched with H_2O at 0°C, and extracted with CH_2Cl_2 to afford pure **1b** (10.3 g, 74%) after distillation. bp 95.5-96.0 °C/18 mmHg; IR(liquid film) ν_{max}/cm^{-1} 1620(C=N); ^{1}H NMR(CCl_4) δ 0.73(9H, s, Si-CH_3), 2.00(2H, s, CH_2), 3.17(2H, t, *J* = 8.0 Hz, N-CH_2), 4.07(2H, t, *J* = 8.0 Hz, S-CH_2); MS *m/z* 173(M^+, 100%); HRMS: Found: 173.0681. Calcd for $C_7H_{15}NSSi$: 173.0694.

Synthesis of 3-nitropyridines (5) or (6); General procedure: All 3-nitropyridine derivatives (**5**) and (**6**)

were prepared according to the procedure given below. As an example, the synthesis of 5-(3-methyl-5-isoxazolyl)-3-nitro-6-phenyl-2-pyridone (**5c**) and 2-ethoxy-5-(3-methyl-5-isoxazolyl)-3-nitro-6-phenyl-pyridine (**6c**) was shown. A 15% solution of *n*-BuLi (4.70 g, 11 mmol) in hexane was added to a solution of 3-methyl-5-trimethylsilylmethylisoxazole (**1c**) (1.69 g, 10 mmol) in THF (80 mL) at -80°C with stirring under nitrogen atmosphere (in the reaction of **1a**, LDA was used instead of *n*-BuLi). After 1 h stirring at the same temperature, benzonitrile (**2a**) (1.03 g, 10 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 (**3c**). After cooling to -80°C, ethyl 3-ethoxy-2-nitropropenoate (**4**) (1.73 g, 10 mmol) was slowly added to the solution of **3c**, and the mixture was stirred for 1 h at -80°C and then for 12 h at rt (in the reaction of **3a**, 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 chromatographed on silica gels eluting with ether to afford pure **5c** (2.38 g, 80%) and **6c** (0.65 g, 20%) (see Table 1). **5c**: mp 265.0-269.0°C (decomp); IR(KBr) ν_{max}/cm^{-1} 3060(N-H), 1675(C=O), 1591, 1319(NO_2); ^{1}H NMR($CDCl_3$) δ 2.21(3H, s, Isoxazolyl-CH_3), 5.51(1H, s, Isoxazolyl-H), 7.46-7.65(5H, m, Ph-H), 8.86(1H, s, 4-H), 11.43(1H, br s, 1-NH); MS: *m/z* 297(M^+, 100%); HRMS: Found 297.0745. Calcd for $C_{15}H_{11}N_3O_4$ 297.0748. **6c**: mp 129.3-130.5°C; IR(KBr) ν_{max}/cm^{-1} 1603($Ar_{C=C}$), 1564, 1247(NO_2); ^{1}H NMR ($CDCl_3$) δ 1.46(3H, t, *J* = 6.6 Hz, OCH_2CH_3), 2.20(3H, s, Isoxazolyl-CH_3), 4.63(2H, q, *J* = 6.6 Hz, OCH_2CH_3), 5.59(1H, s, Isoxazolyl-H), 7.40(5H, s-like, Ph-H), 8.57(1H, s, 4-H); MS: *m/z* 325(M^+, 100%); HRMS: Found: 325.1079. Calcd for $C_{17}H_{15}N_3O_4$: 325.1062.

3-Nitro-6-phenyl-5-(2-pyridyl)-2-pyridone (**5a**): mp 200.1-201.5°C(decomp); IR(KBr) ν_{max}/cm^{-1} 1680 (C=O), 1597, 1382(NO_2); ^{1}H NMR(acetone-d_6) δ 6.83(1H, d, *J* = 8.0 Hz, Py-H), 7.20(1H, dd, *J* = 6.0, 5.0 Hz, Py-H), 7.40(5H, s-like, Ph-H), 7.48(1H, dd, *J* = 8.0, 6.0 Hz, Py-H), 8.57(1H, d, *J* = 5.0 Hz, Py-H), 8.77(1H, s, 4-H), 11.68(1H, br s, 1-NH); MS(FAB): *m/z* 294(M + H, 65%); HRMS(FAB): Found: 294.0880. Calcd for $C_{16}H_{12}N_3O_3$ (M + H): 294.0878.

3-Nitro-6-phenyl-5-(2-thiazolinyl)-2-pyridone (5b): mp 175.9-176.3°C; IR(KBr) ν_{max}/cm^{-1} 3455, 1681(C=O), 1625, 1571, 1334(NO_2) cm^{-1}; ^{1}H NMR($CDCl_3$) δ 3.52 (2H, t, *J* = 8.0 Hz, N-CH_2), 4.70 (2H, t, *J* = 8.0 Hz, S-CH_2), 7.54-7.66(5H, s-like, Ph-H), 8.78(1H, s, 4-H), 11.6(1H, br s, 1-H); MS *m/z* 302(M + 1, 100%); HRMS: Found: 301.0501. Calcd for $C_{14}H_{11}N_3O_3S$: 301.0521.

5-*N,N*-Dimethylcarbamoyl-3-nitro-6-phenyl-2-pyridone (5d): mp 228.6-228.8°C; IR(KBr) ν_{max}/cm^{-1}

1670(C=O), 1637, 1554, 1330(NO_2) cm^{-1}; ^1H NMR($CDCl_3$)δ 2.43(3H, s, NCH_3), 2.84(3H, s, NCH_3), 7.54-8.50(5H, m, Ph-H), 8.15(1H, s, 4-H), 10.61(1H, br s, 1-NH); MS(FAB) *m/z* 288(M + H, 18%), 99(100%); HRMS(FAB): Found: 288.0987. Calcd for $C_{14}H_{14}N_3O_4$ (M + H): 288.0985.

2-Ethoxy-5-*N*,*N*-dimethylcarbamoyl-3-nitro-6-phenylpyridine (6d): mp 118.7-119.6°C; IR(KBr) ν_{max}/cm^{-1} 1635(C=O), 1558, 1336(NO_2) cm^{-1}; ^1H NMR($CDCl_3$) δ1.24(3H, t, *J* = 7.8 Hz, OCH_2CH_3), 2.43(3H, s, NCH_3), 2.88(3H, s, NCH_3), 4.63(2H, q, *J* = 7.8 Hz, OCH_2CH_3), 7.25-7.70(5H, m, Ph-H), 8.19(1H, s, 4-H); MS m/z 315(M^+, 51%)**;** HRMS: Found: 315.1207. Calcd for $C_{16}H_{17}N_3O_4$: 315.1218.

***t*-Butyl 6-Ethoxy-5-nitro-2-(2-pyridyl)nicotinate (6e)**: mp 110.5-111.6°C; IR(KBr) ν_{max}/cm^{-1} 1710(C=O), 1602, 1562, 1388(NO_2) cm^{-1}; ^1H NMR($CDCl_3$) δ 1.33[9H, s, $OC(CH_3)_3$], 1.45(3H, t, *J* = 7.8 Hz, OCH_2CH_3), 4.45(2H, q, *J* = 7.8 Hz, OCH_2CH_3), 7.03-8.40(4H, m, 2-Py-H), 8.04(1H, s, 4-H); MS *m/z* 345(M^+, 11%), 245(100%); HRMS: Found: 345.1325. Calcd for $C_{17}H_{19}N_3O_5$: 345.1325. *Anal.* Calcd for $C_{17}H_{19}N_3O_5$: C, 59.12; H, 5.55; N, 12.17. Found: C, 58.87; H, 5.90; N, 11.92.

Crystal data for 6e: $C_{17}H_{19}N_3O_5$, F.W. = 319.36, monoclinic, space group $P2_1/a$ (#14), *a* = 8.294(5), *b* = 21.993(2), *c* = 9.873(3) Å, β = 103.62(4)°, *V* = 1750(1) $Å^3$, *Z* = 4, D_{calc} = 1.310 g/cm^3, μ(MoK_α) = 0.92 cm^{-1}, crystal dimensions 0.32 x 0.36 x 0.86 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 ω/2θ scan technique to a maximum 2θ value of 55.0°. Of the 4408 reflections which were collected, 4135 were unique (R_{int} = 0.032). The structure was solved by direct methods (SIR88).[25] 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 1519 observed reflections [$I > 3.00\ \sigma(I)$] and 303 variable parameters and converged with unweighted and weighted agreement factors of *R* (0.046) and R_w (0.052). All calculations were performed using the TEXSAN[26] crystallographic software package of Molecular Structure Corporation.

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