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A Convenient Synthesis of Pyridoxine[1)]

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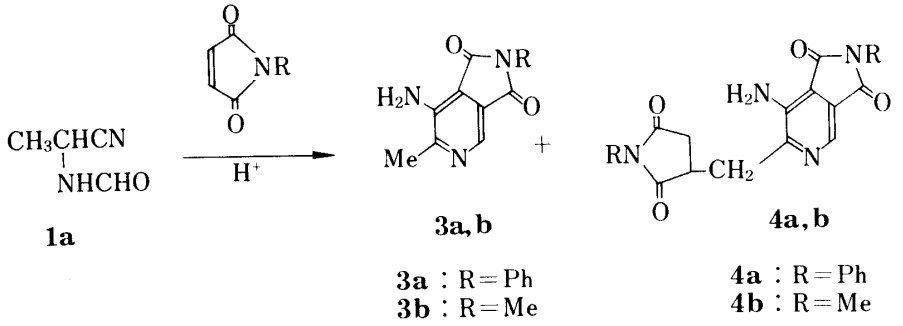
A novel and convenient synthesis of pyridoxine starting from *N*-(1-cyanoethyl)formamide is described. The reaction of *N*-(1-cyanoethyl)acylamides with olefins in the presence of an acid catalyst gave 3-amino-2-methylpyridines. Similar reaction of *N*-(1-cyanoethyl)formamide with fumaronitrile in the presence of trifluoroacetic acid afforded 5-amino-6-methylpyridine-3,4-dicarbonitrile, which was easily converted to pyridoxine by reduction and diazotization.

Keywords——*N*-(1-cyanoethyl)acylamide; fumaronitrile; 3-amino-2-methylpyridine; 3-cyano-2-propen-1-yl acetate; pyridoxine

Many synthetic methods for 4,5-disubstituted 3-amino-2-methylpyridines, important intermediates in the synthesis of pyridoxine, have been reported.[2)] These methods, however, are not satisfactory for large-scale production because they involve multiple steps and troublesome procedures. In the previous paper, we reported a new and convenient method for the synthesis of 3-amino-3-phenylpyridines and ethyl 3-aminopyridine-2-carboxylates from 2-acylaminonitriles and olefins.[3)] This paper deals with a facile synthetic approach to 3-amino-2-methylpyridines by the reaction of *N*-(1-cyanoethyl)acylamides with olefins in the presence of an acid catalyst. We also report the application of the above cyclization reaction to the synthesis of pyridoxine.

When *N*-(1-cyanoethyl)formamide (**1a**) was allowed to react with *N*-phenylmaleimide (**2a**) in 1,2-dichloroethane in the presence of trifluoroacetic acid, 7-amino-6-methyl-1,3-dioxo-2-phenyl-1,3-dihydropyrrolo[3,4-*c*]pyridine (**3a**) and 7-amino-6-(2,5-dioxo-1-phenylpyrrolidin-3-yl)methyl-1,3-dioxo-2-phenyl-1,3-dihydropyrrolo[3,4-*c*]pyridine (**4a**) were obtained in 22 and 38% yields, respectively. Treatment of *N*-phenylmaleimide with a two- or three-fold molar excess of **1a** in the presence of trifluoroacetic acid gave **3a** in 78% yield without formation of **4a**. The yields of **4a** were found to vary depending upon the concentration of *N*-phenylmaleimide in the reaction mixture. These results are summarized in Table I.

The structure of the product (**3a**) was confirmed by its elemental analysis, and infrared (IR), mass and nuclear magnetic resonance (NMR) spectra. The structure **3a** was further confirmed by the fact that the hydrolysis of **3a** with 10% hydrochloric acid afforded 5-amino-6-methylpyridine-3,4-dicarboxylic acid.[4)] The molecular formula of **4a** was found to be $C_{24}H_{18}N_4O_4$ on the basis of its elemental analysis and mass spectrum. The IR spectrum of **4a** showed characteristic peaks at 1750 and 1700 cm^{-1} attributable to carbonyl groups. The ^1H-NMR spectrum of **4a** showed no signal due to a methyl proton, but two pairs of ABX-type signals at δ 2.85 (1H, dd, J=18.5, 5.5 Hz), 3.19 (1H, dd, J=18.5, 9 Hz), 3.60 (1H, m), 3.33 (1H, dd, J=17.5, 4 Hz) and 3.48 (1H, dd, J=17.5, 5.5 Hz). This observation suggests the presence of CH_2–CH units in the molecule. Compound **4a** was assigned as 7-amino-6-(2,5-dioxo-1-phenylpyrrolidin-3-yl)methyl-1,3-dioxo-2-phenyl-1,3-dihydropyrrolo[3,4-*c*]pyridine on the basis of the above observations. Treatment of **3a** with *N*-phenylmaleimide in the presence of trifluoroacetic acid gave **4a** in 45% yield. From these results, the formation of **4a** can be explained in terms of the Michael-type addition of the methylpyridine (**3a**).



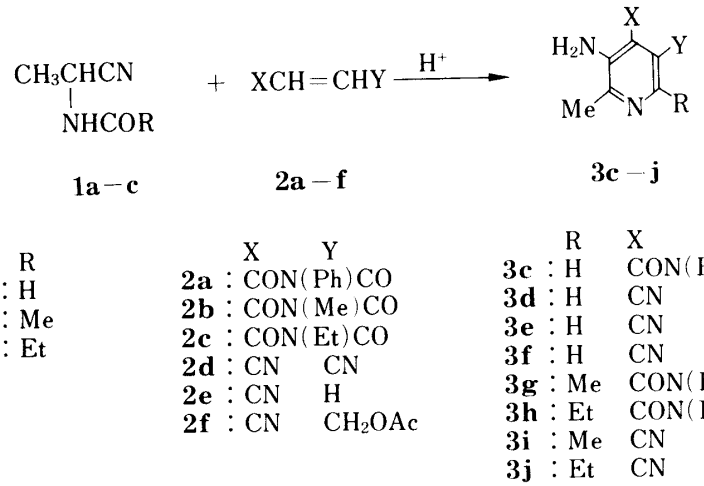


Chart 1

TABLE I. Reaction of **1a** with *N*-Phenylmaleimide (**2a**)

Run	Solvent (ml/10 mmol)	Reaction					Yield (%)	
		Temp. (°C)	Time (h)	Mol ratio of **1a** : **2a** : TFA[a]			**3a**	**4a**
1	—	100	17	1	1	0.1	22	38
2	EDC[b] (5)	100	15	1	1	0.1	28	32
3	EDC (30)	100	30	1	1	1	37	—
4	EDC (5)	100	30	2	1	0.5	78	—

a) TFA: trifluoroacetic acid.
b) EDC: 1,2-dichloroethane.

Similar reaction of **1a** with *N*-methylmaleimide (**2b**) in the presence of trifluoroacetic acid gave 7-amino-2,6-dimethyl-1,3-dioxo-1,3-dihydropyrrolo[3,4-*c*]pyridine (**3b**) and 7-amino-2-methyl-(2,5-dioxo-1-methylpyrrolidin-3-yl)methyl-1,3-dihydropyrrolo[3,4-*c*]pyridine (**4b**) in 13 and 25% yields, respectively. When **1a** was refluxed in acrylonitrile (**2e**) in the presence of trifluoroacetic acid, 3-amino-2-methylpyridine-4-carbonitrile (**3e**) was obtained in 12% yield. The ^{1}H-NMR spectrum of **3e** showed pyridine ring proton signals at δ 7.17 (d, J=5 Hz) and δ 7.95 (d, J=5 Hz). Thus, the location of the cyano group at the 4-position of the pyridine ring is reasonable.

Table II. Preparation of 3-Amino-2-methylpyridines (3)

3	R	X	Y	Yield 3 (%)	Unchanged 2 (%)
a	H	CO–N(Ph)–CO		37	36
b	H	CO–N(Me)–CO		25	44
c	H	CO–N(Et)–CO		25	36
d	H	CN	CN	42	28
e	H	CN	H	12	—
f	H	CN	CH_2OAc	10	51
g	Me	CO–N(Ph)–CO		16	50
h	Et	CO–N(Ph)–CO		20	68
i	Me	CN	CN	13	48
j	Et	CN	CN	16	35

Table III. Reaction of **1a** with Fumaronitrile

Run	Mol eq of 1a : 2a : Acid	Yield 3d (%) (Based on 2d)	Recovery 1a (%)	Recovery 2d (%)
1	5 : 1 : 0.25 (TFA)[a]	67	62	1
2	3.5 : 1 : 0.05 (TFA)	39	34	13
3	1 : 1 : 0.05 (TFA)	42	10	29
4	1 : 2.5 : 0.05 (TFA)	36[c]	1	61
5	3.5 : 1 : 0.2 (Oxalic)	34	43	39
6	3.5 : 1 : 0.4 (Oxalic)	36	27	36
7	3.5 : 1 : 0.1 (CAA)[b]	37	51	19

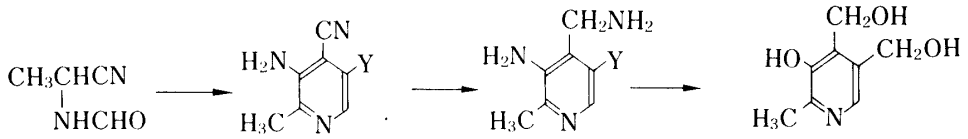
a) TFA: trifluoroacetic acid.
b) CAA: chloroacetic acid.
c) Based on **1a**.

Similarly, *N*-(1-cyanoethyl)acylamides (**1a**—**c**) were treated with olefins (**2a**—**e**) in the presence of the acid to give the corresponding 3-amino-2-methylpyridines (**3c**—**j**). These results are listed in Table II.

Subsequently, the application of the above reaction to the synthesis of pyridoxine was examined. The reaction of *N*-(1-cyanoethyl)formamide (**1a**) with fumaronitrile (**2d**) in the presence of trifluoroacetic acid gave 5-amino-6-methylpyridine-3,4-dicarbonitrile (**3d**) in 42% yield without formation of the **4a**-type compound. The reaction proceeded with a catalytic amount of the acid. Oxalic acid and chloroacetic acid could be used as the acid catalyst in place of trifluoroacetic acid. When the mixture of **1a**, **2a** and trifluoroacetic acid was heated for a long time, **1a** was hydrolyzed into 2-formamidopropionamide. Therefore, it is preferable to react a two- or three-fold molar excess of **1a** with fumaronitrile.

Pyridoxine[5] was obtained from **3d** in good yield by the known methods. Catalytic hydrogenation of **3d** on 5% palladium charcoal in hydrochloric acid–methanol afforded 3-amino-4,5-bis(aminomethyl)-2-methylpyridine trihydrochloride (**5a**) in 75% yield. Treatment of **5a** with nitrous acid gave pyridoxine in 75% yield.[6]

When 3-cyano-2-propen-1-yl acetate (**2f**) was heated with **1a** in the presence of oxalic acid, 5-acetoxymethyl-3-amino-2-methylpyridine-4-carbonitrile (**3f**) was obtained in low yield. The acetate (**2f**) seemed to be less reactive than fumaronitrile (**2d**). The structure of the product (**3f**) was confirmed by the fact that the catalytic reduction of **3f** under acidic



1a **3** **5** **6**

3d : Y = CN
3f : Y = CH_2OAc
5a : Y = CH_2NH_2
5b : Y = CH_2OH

Chart 2

conditions afforded 3-amino-4-aminomethyl-5-hydroxymethyl-2-methylpyridine (**5b**) dihydrochloride.[7]

In summary, 3-amino-2-methylpyridines could be prepared from *N*-(1-cyanoethyl)-acylamides (**1a**—**c**) and olefins having an electron-withdrawing group under mild conditions. This process appears to provide a useful method for the synthesis of pyridoxine. The mechanism of this reaction is now under detailed investigation.

Experimental

All melting points and boiling points are uncorrected. IR spectra were recorded on a Hitachi model 260 spectrometer. ^{1}H-NMR spectra were recorded on a JEOL model JNM-PMX 60 at 60 MHz or a Varian XL-200 spectrometer at 200 MHz. Chemical shifts are expressed as ppm downfield from tetramethylsilane as an internal standard. The following abbreviations are used: s = singlet, d = doublet, t = triplet, m = multiplet, br = broad and dd = double doublet. Mass spectra (MS) were measured with a JEOL TMS D 300 mass spectrometer.

Preparation of *N*-(1-Cyanoethyl)acylamides (1a—c)——*N*-(1-Cyanoethyl)formamide (**1a**) and *N*-(1-cyanoethyl)acetamide (**1b**) were prepared from lactonitrile according to the literature.[8] *N*-(1-Cyanoethyl)propionamide (**1c**) was prepared from **1a** and propionic anhydride by a modification of the reported method.[9] The data for **1a**—**c** are given below.

1a: bp 137—139 °C (4 mmHg). Lit.[8] bp 97 °C (0.5 mmHg). **1b**: mp 97—98 °C (colorless prisms from EtOH). Lit.[8] mp 98 °C. **1c**: mp 65—66 °C (colorless prisms from EtOH). IR ν_{max}^{KBr} cm^{-1}: 3300, 2240, 1640. ^{1}H-NMR ($CDCl_3$) δ: 1.16 (3H, t, J = 7 Hz, CH_3), 1.52 (3H, d, J = 7 Hz, CH_3), 2.32 (2H, q, J = 7 Hz, CH_2), 5.00 (1H, m, CH), 6.55 (1H, br, NH).

3-Cyano-2-propen-1-yl Acetate (2f)——A solution of 4-bromo-2-butenenitrile[10] (25 g) and potassium acetate (20 g) in acetic acid (100 ml) was refluxed for 1 h. Afrer removal of the acetic acid, the residue was distilled under reduced pressure to give **2f** as a mixture of the *cis* and *trans* products, bp 90—93 °C (10 mmHg).

Reaction of *N*-(1-Cyanoethyl)formamide (1a) with *N*-Substituted Maleimides (2a, b)——A solution of *N*-(1-cyanoethyl)formamide (**1a**) (1.96 g, 20 mmol), an *N*-substituted maleimide (20 mmol) and trifluoroacetic acid (0.23 g, 2 mmol) in 1,2-dichloroethane (1—50 ml) was heated at 100 °C for 8—16 h. The mixture was poured into water, and was neutralized with 5% aq. $NaHCO_3$. The whole was extracted with $CHCl_3$. The combined extracts were washed with water, dried over Na_2SO_4 and concentrated *in vacuo*. The resulting residue was chromatographed on a silica gel column with $CHCl_3$ as an eluent. From the early part of the fractions, the corresponding 7-amino-6-(1-substituted 2,5-dioxopyrrolidin-3-yl)methyl-1,3-dioxo-1,3-dihydropyrrolo[3,4-*c*]pyridine (**4**) was obtained, while the later part provided the corresponding 7-amino-6-methyl-1,3-dioxo-1,3-dihydropyrrolo[3,4-*c*]pyridine (**3**). The yields of **3** and **4** are listed in Tables I and II. The data for **3a**, **b** and **4a**, **b** are summarized in Table IV.

Reaction of 3a with *N*-Phenylmaleimide (2a)——A solution of **3a** (2.53 g, 10 mmol), **2a** (5.19 g, 30 mmol) and trifluoroacetic acid (0.23 g, 2 mmol) in 1,2-dichloroethane (10 ml) was refluxed for 16 h. The reaction mixture was worked up as described above to give **4a** (1.92 g, 45%).

General Procedure for the Preparation of 3c—j——A solution of a *N*-(1-cyanoethyl)acylamide (**1a**—**c**) (10 mmol), an olefin (**2a**—**e**) (10 mmol) and trifluoroacetic acid (1 mmol) in 1,2-dichloroethane (2—50 ml) was refluxed for 16—48 h. After removal of the solvent, the residue was neutralized with 5% aq. $NaHCO_3$ solution, and then the whole was extracted with $CHCl_3$. The extracts were washed with water, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed on a silica gel column. Elution with $CHCl_3$ gave a 3-aminopyridine. The yields of **3** are listed in Table II. The data for **3c**—**j** are summarized in Table V.

Pyridoxine——From **3d**: A mixture of **3d** (1.58 g, 10 mmol), 5% Pd-C (1.6 g) and conc. HCl (6.4 ml) in 98% aq. MeOH (160 ml) was stirred under a stream of hydrogen for 3.5 h at room temperature. After removal of the

TABLE IV. Physicochemical Data for **3a**, **3b**, **4a** and **4b**

Compd. No.	Recryst. solvent mp (°C)	MS *m/e*	IR cm^{-1}	^{1}H-NMR ($CDCl_3$) *J*=Hz	Formula *Anal.* Calcd (Found) (%) C	H	N
3a	AcOEt (Needles) 225	253 (M^+)	1740 1700	2.53 (3H, s, CH_3), 6.51 (2H, br, NH_2), 7.52 (5H, s, C_6H_5), 8.21 (1H, s, ring proton)	$C_{14}H_{11}N_3O_2$ 66.40 (66.49)	4.38 4.43	16.59 16.49)
3b	AcOEt (Needles) 205	191 (M^+)	1755 1700	2.50 (3H, s, CH_3), 3.06 (3H, s, NCH_3), 6.10 (2H, br, NH_2), 8.11 (1H, s, ring proton)	$C_9H_9N_3O_2$ 56.53 (56.85)	4.74 4.88	21.98 21.88)
4a	AcOEt (Needles) 300	426 (M^+)	1750 1700	2.85 (1H, dd, *J*=5.5, 18.5), 3.19 (1H, dd, *J*=9, 18.5), 3.60 (1H, m), 3.33 (1H, dd, *J*=4, 17.5), 3.48 (1H, dd, *J*=5.5, 17.5), 5.43 (2H, br, NH_2), 8.45 (1H, s, ring proton)	$C_{24}H_{18}N_4O_4$ 67.60 (67.48)	4.24 4.29	13.14 13.13)
4b	AcOEt (Needles) 235	302 (M^+)	1760 1700	3.02 (3H, s, NCH_3), 3.07 (3H, s, NCH_3), 5.17 (2H, br, NH_2), 8.15 (1H, s, ring), 2.32 (1H, dd, *J*=18, 6.5), 3.15 (1H, dd, *J*=5, 16), 3.20 (1H, m)	$C_{14}H_{14}N_4O_4$ 55.62 (55.50)	4.67 4.50	18.58 18.47)

TABLE V. Physicochemical Data for 3-Amino-2-methylpyridines (**3c**—**j**)

Compd. No.	Recryst. solvent mp (°C)	MS *m/e*	IR cm^{-1}	^{1}H-NMR ($CDCl_3$) *J*=Hz	Formula *Anal.* Calcd (Found) (%) C	H	N
3c	AcOEt (Plates) 122	205 (M^+)	1750 1700	2.58 (3H, s, CH_3), 1.28 (3H, t, CH_3), 3.73 (2H, q, CH_2), 5.33 (2H, br, NH_2), 8.35 (1H, s, ring proton), ($CDCl_3$)	$C_{10}H_{11}N_3O_2$ 58.53 (58.52)	5.40 5.52	20.48 20.29)
3d	AcOEt (Needles) 203	158 (M^+)	2220	2.50 (3H, s, CH_3), 6.8—7.1 (2H, br, NH_2), 8.23 (1H, s, ring), (DMSO-d_6)	$C_8H_6N_4$ 60.75 (60.66)	3.83 3.85	35.43 35.45)
3e	Acetone (Plates) 141—142	133 (M^+)	2220	2.50 (3H, s, CH_3), 4.4—4.7 (2H, br, NH_2), 7.17 (1H, d, *J*=5), 7.95 (1H, d, *J*=5), ($CDCl_3$)	$C_7H_7N_3$ 63.14 (63.10	5.30 5.20	31.56 31.33)
3f	$CHCl_3$ (Prisms) 110—112		2220 1725	2.14 (3H, s, $COCH_3$), 2.47 (3H, s, CH_3), 4.5—4.9 (2H, br, NH_2), 5.12 (2H, s, CH_2), 7.93 (1H, s, ring)	$C_{10}H_{11}N_3O_2$ 58.53 (58.29)	5.40 5.42	20.48 20.37)
3g	AcOEt (Needles) 262	267 (M^+)	1740 1700	2.49 (3H, s, CH_3), 2.60 (3H, s, CH_3), 6.2—6.4 (2H, br, NH_2), 7.51 (5H, s, C_6H_5), (DMSO-d_6)	$C_{15}H_{13}N_3O_2$ 67.40 (67.19)	4.90 4.90	15.72 15.73)
3h	AcOEt (Plates) 235	281 (M^+)	1740 1700	2.50 (3H, s, CH_3), 6.2—6.4 (2H, br, NH_2), 7.50 (5H, s, C_6H_5), 1.29 (3H, t, CH_3), (DMSO-d_6)	$C_{16}H_{15}N_3O_2$ 68.31 (68.50	5.38 5.35	14.94 14.89)
3i	(Iso-Pr)$_2$O (Needles) 217	172 (M^+)	2230	2.42 (3H, s, CH_3), 2.49 (3H, s, CH_3), 6.52 (2H, br, NH_2), (DMSO-d_6)	$C_9H_8N_4$ 62.77 (62.80	4.68 4.70	32.56 32.54)
3j	(Iso-Pr)$_2$O (Needles) 162	186 (M^+)	2230	2.49 (3H, s, CH_3), 1.29 (3H, t, CH_3), 2.71 (2H, q, CH_2), 6.48 (2H, br, NH_2), (DMSO-d_6)	$C_{10}H_{10}N_4$ 64.50 (64.97)	5.41 5.55	30.08 29.97)

catalyst by filtration, the filtrate was concentrated to dryness. The residue was triturated with EtOH to give crude 3-amino-4,5-bis(aminomethyl)-2-methylpyridine trihydrochloride (**5a**). Recrystallization from 90% EtOH afforded **5a** (2.0 g, 75%), mp 300 °C (colorless prisms). Lit.[6] 300 °C. *Anal.* Calcd for $C_8H_7Cl_3N_4$: C, 34.86; H, 6.22; N, 20.33. Found; C, 35.14; H, 6.35; N, 20.29. A solution of sodium nitrite (4.2 g) in water (45 ml) was added to a mixture of **5a** (2.72 g, 10 mmol), H_2SO_4 (8 g) and water (100 ml) at 90 °C during about 1 h. The temperature of the mixture was kept at 90 °C and stirring was continued for 2 h after addition was complete. $BaCl_2$ (1.7 g) was then added to the reaction mixture. The Ba salts were removed by filtration, and washed with water. The combined filtrates were evaporated to dryness. The residue was purified by recrystallization from EtOH. Material insoluble in the hot solvent was removed by filtration, and the filtrate was evaporated to give pyridoxine hydrochloride (1.52 g, 75%), which was proved to be identical with an authentic sample in mp and by spectral comparisons.

From **3f**: Hydrogen gas was bubbled through a stirred mixture of **3f** (2.05 g, 10 mmol), 5% Pd-C (0.4 g) and conc. HCl (3 ml) in 98% aq. MeOH (120 ml) for 1 h at room temperature. The catalyst was filtered. 0.2 N HCl (70 ml) was added to the filtrate, and the mixture was stirred for 1 h at 80 °C. After removal of the solvent, the residue was recrystallized from EtOH to give 3-amino-4-aminomethyl-5-hydroxymethylpyridine dihydrochloride (**5b**) (2.60 g, 88%), mp 257 °C (colorless prisms). *Anal.* Calcd for $C_8H_{15}Cl_2N_3O$: C, 40.01; H, 6.30; Cl, 29.53; N, 17.50. Found: C, 39.81; H, 6.03; Cl, 29.47; N, 17.10. Treatment of **5b** with nitrous acid in a manner similar to that described above gave pyridoxine hydrochloride.

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