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A One-Pot Synthesis of 3-Aminopyridines

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The reaction of *N*-(cyanophenylmethyl)acylamides (**1**) with olefins (**2**) in the presence of trifluoroacetic acid gave the corresponding 3-amino-2-phenylpyridines (**3**) in good yields.

Similar reaction of ethyl 2-acylamino-2-cyanoacetates (**4**) with olefins in the presence of trifluoroacetic acid afforded ethyl 3-aminopyridine-2-carboxylates (**5**) in a one-pot procedure. The mechanism of the reaction is discussed.

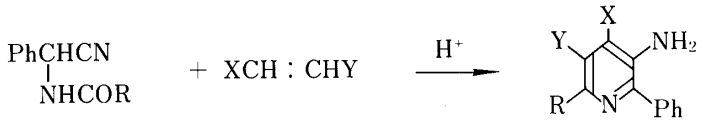
Keywords——3-amino-2-phenylpyridine; *N*-(cyanophenylmethyl)acylamide; one-pot synthesis; ethyl 2-acylamino-2-cyanoacetate; ethyl 3-aminopyridine-2-carboxylate; 5-aminooxazole

Many reports have been published on the preparation of 3-aminopyridine derivatives.[1] However, few studies have been carried out on the synthesis of 3-aminopyridine derivatives involving carbon–carbon bond formation.[2]

Omura *et al.* reported the preparation of 5-amino-6-phenylpyridine-3,4-dicarboxylic acid in 4 steps starting from 3-cyano-4-ethoxycarbonyl-6-phenyl-2-pyridone.[3] Gadekar *et al.* reported the synthesis of 3-aminopyridine-2,4,5-tricarboxylic acid from 3-cyano-4-ethoxycarbonyl-6-methyl-2-pyridone.[4] These methods, however, were not satisfactory because of the multiple steps and severe reaction conditions required.

We report here a new and covenient method for the synthesis of 3-amino-2-phenylpyridines in one step from *N*-(cyanophenylmethyl)acylamides by reaction with olefins in the presence of trifluoroacetic acid. We also report the cycloaddition reaction of ethyl 5-aminooxazole-4-carboxylate with *N*-phenylmaleimide.

When *N*-(cyanophenylmethyl)formamide (**1a**) was reacted with *N*-phenylmaleimide (**2a**) in the presence of trifluoroacetic acid, 7-amino-1,3-dioxo-2,6-diphenyl-1,3-dihydropyrrolo[3,4-*c*]pyridine (**3a**) was obtained in 72% yield. The molecular formula was confirmed to be $C_{19}H_{13}N_3O_2$ by elemental analysis and mass spectroscopy (M^+ *m/e*: 315). The proton nuclear magnetic resonance (^{1}H-NMR) spectrum revealed a singlet at 8.50 ppm (1H) due to the pyridine ring proton and a broad peak at 6.30 ppm (2H) due to the amino group. From these observations, **3a** was assigned as 7-amino-1,3-dioxo-2,6-diphenyl-1,3-dihydropyrrolo[3,4-*c*]pyridine. The structure of **3a** was further confirmed by hydrolysis of **3a** to give 5-amino-6-phenylpyridine-3,4-dicarboxylic acid.[3]



1a, b **2a—c** **3a—e**

1a : R=H
1b : R=CH_3

2a : X, Y=CO–N(Ph)–CO
2b : X, Y=CN
2c : X=CN, Y=H

Chart 1

TABLE I. Preparation of 3-Amino-2-phenylpyridines (**3**)

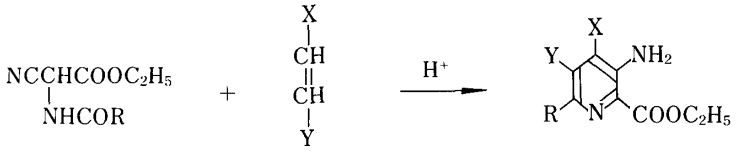
3	R	X	Y	React. time (h)	React. temp. (°C)	mp (°C)	Yield (%)
a	H	CO–N(Ph)–CO		16	100	280	71
b	CH_3	CO–N(Ph)–CO		16	100	255	73
c	H	CN	CN	16	100	176	42
d	CH_3	CN	CN	20	100	136	36
e	H	CN	H	36	80	147	34

TABLE II. Preparation of Ethyl 3-Aminopyridine-2-carboxylates (**5**)

5	R	X	Y	Acid	(mol eq to **4**)	mp (°C)	Yield (%)
a	H	CO–N(Ph)–CO		CF_3COOH	(0.2)	200	67
b	CH_3	CO–N(Ph)–CO		HCOOH	(4.0)		67
b	CH_3	CO–N(Ph)–CO		$(COOH)_2$	(0.5)	198	63
b	CH_3	CO–N(Ph)–CO		CF_3COOH	(1.0)		67
b	CH_3	CO–N(Ph)–CO		CF_3COOH	(0.1)		75
c	H	CN	CN	CF_3COOH	(0.1)	140	14
d	CH_3	CN	CN	CF_3COOH	(0.1)	139	10
e	H	CN	H	CF_3COOH	(0.1)	118	51
f	CH_3	CN	H	CF_3COOH	(0.1)	139	35

Similar reactions of *N*-(cyanophenylmethyl)acylamides (**1**) were attempted with some olefins, and the results are summarized in Table I. Treatment of **1a** with fumaronitrile (**2b**) in the presence of trifluoroacetic acid afforded 5-amino-3,4-dicyano-6-phenylpyridine (**3c**) in 42% yield. Compound **3c** was transformed by hydrolysis to 5-amino-6-phenylpyridine-3,4-dicarboxylic acid. Fumaronitrile seemed to be less reactive than *N*-phenylmaleimide. The reaction of **1a** with acrylonitrile (**2c**) in the presence of trifluoroacetic acid afforded 3-amino-4-cyano-2-phenylpyridine (**3e**) in 34% yield, and did not give 5-amino-3-cyano-6-phenylpyridine. The ^{1}H-NMR spectrum of **3e** revealed pyridine ring protons at 7.25 and 8.15 ppm, having a coupling constant of $J=5$ Hz. From these observations, the structure of **3e** was determined to be 3-amino-4-cyano-2-phenylpyridine (**3e**).

Next, the reaction of ethyl 2-acylamino-2-cyanoacetates (**4**) with olefins was carried out. When ethyl 2-formylamino-2-cyanoacetate (**4a**) was heated with *N*-phenylmaleimide in the presence of trifluoroacetic acid, **5a** was obtained in 68% yield. The structure of **5a** was assumed to be 7-amino-6-ethoxycarbonyl-1,3-dioxo-2-phenyl-1,3-dihydropyrrolo[3,4-*c*]-pyridine on the basis of spectral and analytical data, and the structure was finally confirmed by the hydrolysis of **5a** to give 3-aminopyridine-2,4,5-tricarboxylic acid.[4]



4a, b **2a—c** **5a—e**

4a : R=H
4b : R=CH_3

Chart 2

The reaction proceeded with a catalytic amount of trifluoroacetic acid (0.05—0.1 mol eq to **4**). Some other acids could be used as catalysts in place of trifluoroacetic acid, and the results are summarized in Table II. Thus, compounds (**5a**, **b**) were obtained in good yields by using formic acid, oxalic acid and trifluoroacetic acid as catalysts, but **5** could not be isolated in the absence of an acid catalyst.

Similar reactions of ethyl 2-acylamino-2-cyanoacetates (**4**) with olefins in the presence of trifluoroacetic acid afforded 3-aminopyridine-2-carboxylates (**5**). The reaction of **4a** with acrylonitrile (**3c**) in the presence of the acid afforded ethyl 3-amino-4-cyanopyridine-2-carboxylate (**5e**). The ^{1}H-NMR spectrum of **5e** showed pyridine ring proton signals at 7.48 ppm (d, $J=5$ Hz) and 8.15 ppm (d, $J=5$ Hz). Thus, the location of the cyano group at the 4 position of the pyridine ring is reasonable. These results are listed in Table II.

The mechanism of the formation of 3-aminopyridines was investigated. It is known that 2-acylaminonitriles are cyclized to 5-aminooxazoles in the presence of an acid catalyst.[5] In our experiments, the reaction of ethyl 2-acylamino-2-cyanoacetates (**4**) with olefin in the absence of an acid catalyst resulted in recovery of the starting materials. On the other hand, the reaction of ethyl 5-aminooxazole-4-carboxylate (**6a**), obtained by the method of Sein and Grifantini,[6] with *N*-phenylmaleimide in the presence or in the absence of trifluoroacetic acid gave **5a** in 75% yield. On the basis of these observations, we propose the reaction mechanism shown in Chart 3.

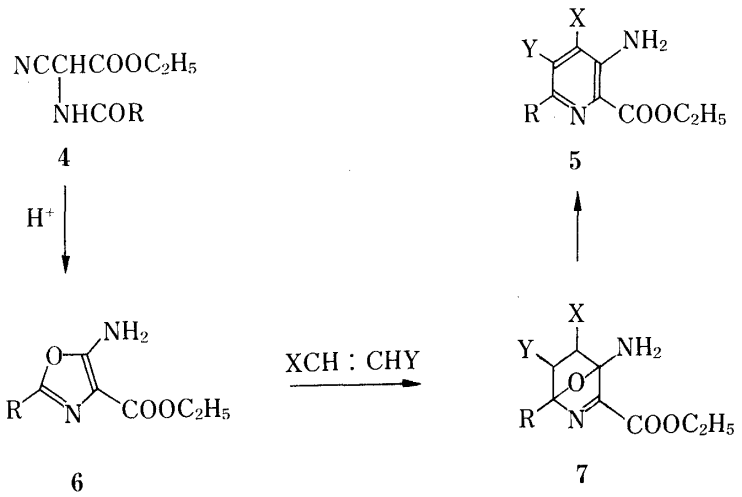


Chart 3

Thus, we have established a one-pot synthesis of 3-amino-2-phenylpyridines and ethyl 3-aminopyridine-2-carboxylates, which are otherwise difficult to obtain, using easily available starting materials.

Experimental

Melting points were taken on a Yanagimoto micro hot-stage mp apparatus, and are uncorrected. Infrared (IR) spectra were taken in KBr disks with a Hitachi model 280 spectrometer. Mass spectra (MS) were measured with a JEOL JMS-D 300 mass spectrometer. ^{1}H-NMR spectra were measured on a JEOL model JNM-PMX 60 spectrometer at 60 MHz, employing tetramethylsilane as an internal standard. The following abbreviations are used: s = singlet, d = doublet, t = triplet, m = multiplet and br = broad.

7-Amino-1,3-dioxo-2,6-diphenyl-1,3-dihydropyrrolo[3,4-*c*]pyridine (3a)——Trifluoroacetic acid (0.11 g, 1 mmol) was added to a solution of *N*-(cyanophenylmethyl)formamide (**1a**) (1.60 g, 10 mmol) and *N*-phenylmaleimide (**2a**) (1.73 g, 10 mmol) in 1,2-dichloroethane (10 ml) under stirring at room temperature. The mixture was refluxed for 16 h. The reaction mixture was neutralized with 5% aq. $NaHCO_3$ solution, and then the whole was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water and dried over Na_2SO_4. Removal of the solvent afforded a crude solid which was chromatographed on silica gel with $CHCl_3$ to give **3a** (2.25 g, 72%), mp 280 °C (yellow needles from AcOEt). IR

ν_{max}^{KBr} cm^{-1}: 1760, 1700. ^{1}H-NMR (DMSO-d_6) δ: 6.30 (2H, br, NH_2), 7.5—7.8 (10H, m, C_6H_5, C_6H_5), 8.50 (1H, s, pyridine ring proton). MS *m/e*: 315 (M^+). *Anal.* Calcd for $C_{19}H_{13}N_3O_2$: C, 72.38; H, 4.13; N, 13.33. Found: C, 72.05; H, 4.10; N, 12.92.

Hydrolysis of 3a——A mixture of **3a** (0.2 g) and 10% aq. HCl (10 ml) was refluxed for 12 h. The reaction mixture was basified with 10% aq. NaOH solution. The whole was shaken with Et_2O, and the upper layer was separated. The aqueous layer was slightly acidified with 10% HCl to deposit a pale yellow powder. Recrystallization of the above powder from 50% EtOH gave 5-amino-6-phenylpyridine-3,4-dicarboxylic acid (**8**), mp 212—215 °C. The IR and NMR spectra of **8** were superimposable on those of an authentic sample.

7-Amino-4-methyl-1,3-dioxo-2,6-diphenyl-1,3-dihydropyrrolo[3,4-*c*]pyridine (3b)——Trifluoroacetic acid (0.11 g, 1 mmol) was added to a solution of *N*-(cyanophenylmethyl)acetamide (**1b**) (1.74 g, 10 mmol) and *N*-phenylmaleimide (1.73 g, 10 mmol) in 1,2-dichloroethane (10 ml) under stirring at room temperature. The mixture was refluxed for 16 h. The reaction mixture was neutralized with 5% aq. $NaHCO_3$ solution, and then the whole was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with water and dried over Na_2SO_4. Removal of the solvent afforded a crude solid which was chromatographed on silica gel with $CHCl_3$ to give **3b** (74%), mp 255 °C (yellow plates from AcOEt). IR ν_{max}^{KBr} cm^{-1}: 1760, 1700. MS *m/e*: 329 (M^+). ^{1}H-NMR (DMSO-d_6) δ: 2.60 (3H, s, CH_3), 6.00 (2H, br, NH_2), 7.4—7.5 (10H, m, C_6H_5, C_6H_5). *Anal.* Calcd for $C_{20}H_{15}N_3O_2$: C, 72.92; H, 4.59; N, 12.76. Found: C, 73.28; H, 4.76; N, 12.75.

5-Amino-3,4-dicyano-6-phenylpyridine (3c)——A solution of *N*-(cyanophenylmethyl)formamide (**1a**) (1.60 g, 10 mmol), fumaronitrile (0.80 g, 10 mmol) and trifluoroacetic acid (0.11 g, 1 mmol) in 1,2-dichloroethane (2 ml) was stirred at 90 °C for 16 h. After removal of the solvent by evaporation, the residue was dissolved in $CHCl_3$. The $CHCl_3$ layer was washed with 5% $NaHCO_3$ aq. solution and water. The organic layer was chromatographed on a silica gel column with $CHCl_3$ as an eluent to give **3c** (0.93 g, 42%) as pale yellow needles, mp 176 °C (isopropyl ether). IR ν_{max}^{KBr} cm^{-1}: 2220. ^{1}H-NMR ($CDCl_3$) δ: 5.10 (2H, br, NH_2), 7.65 (5H, m, C_6H_5), 8.42 (1H, s, pyridine ring proton). MS *m/e*: 220 (M^+). *Anal.* Calcd for $C_{13}H_8N_4$: C, 70.90; H, 3.66; N, 25.44. Found: C, 71.19; H, 3.83; N, 25.53.

5-Amino-3,4-dicyano-2-methyl-6-phenylpyridine(3d)——A mixture of **1b** (1.74 g, 10 mmol), fumaronitrile (0.80 g, 10 mmol), trifluoroacetic acid (0.11 g, 1 mmol) and 1,2-dichloroethane (2 ml) was refluxed for 16 h, then worked up in the manner described above to afford **3d** (0.85 g, 36%) as pale yellow needles, mp 136 °C (isopropyl ether). IR ν_{max}^{KBr} cm^{-1}: 2220. ^{1}H-NMR ($CDCl_3$) δ: 2.70 (3H, s, CH_3), 4.90 (2H, br, NH_2), 7.60 (5H, s, C_6H_5). MS *m/e*: 234 (M^+). *Anal.* Calcd for $C_{14}H_{10}N_4$: C, 71.78; H, 4.30; N, 23.92. Found: C, 72.11; H, 4.46; N, 23.58.

3-Amino-4-cyano-2-phenylpyridine (3e)——A mixture of **1a** (1.60 g, 10 mmol), trifluoroacetic acid (0.11 g, 1 mmol) and acrylonitrile (20 ml) was refluxed for 36 h. The mixture was concentrated under reduced pressure, and the residue was dissolved in $CHCl_3$. The $CHCl_3$ solution was washed with 5% $NaHCO_3$ aq. solution and water. The organic layer was chromatographed on a silica gel column with $CHCl_3$ as an eluent to give **3e** (0.67 g, 34%) as pale yellow needles, mp 147 °C (isopropyl ether). IR ν_{max}^{KBr} cm^{-1}: 2220. ^{1}H-NMR ($CDCl_3$) δ: 4.70 (2H, br, NH_2), 7.25 (1H, d, J=5 Hz, pyridine ring proton), 8.15 (1H, d, J=5 Hz, pyridine ring proton). MS *m/e*: 195 (M^+). *Anal.* Calcd for $C_{12}H_9N_3$: C, 73.82; H, 4.65; N, 21.52. Found: C, 73.91; H, 4.67; N, 21.46.

Ethyl 5-Aminooxazole-4-carboxylate (6a)——The oxazole (**6a**) was prepared in 67% yield from ethyl 2-formylamino-2-cyanoacetate (**4a**) according to the method developed by Grifantini and Sein.[6]

7-Amino-6-ethoxycarbonyl-1,3-dioxo-2-phenyl-1,3-dihydropyrrolo[3,4-*c*]pyridine (5a)——Reaction of Ethyl 2-Formylamino-2-cyanoacetate (**4a**) with *N*-Phenylmaleimide (**2a**): A solution of **4a** (1.58 g, 10 mmol), **2a** (1.73 g, 10 mmol) and trifluoroacetic acid (0.11 g, 1 mmol) in 1,2-dichloroethane (15 ml) was refluxed for 20 h. $CHCl_3$ (50 ml) and water (30 ml) were added to the reaction mixture. The whole was carefully basified with 5% $NaHCO_3$ aq. solution and the organic layer was washed with water. After removal of the solvent by evaporation, the residue was recrystallized from ethyl acetate to give **5a** (2.10 g, 68%) as yellow needles, mp 199—200 °C. IR ν_{max}^{KBr} cm^{-1}: 1740, 1700. MS *m/e*: 311 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.48 (3H, t, J=8 Hz, CH_3), 4.55 (2H, q, CH_2), 7.20 (2H, br, NH_2), 7.50 (5H, s, C_6H_5), 8.65 (1H, s, pyridine ring proton). *Anal.* Calcd for $C_{16}H_{13}N_3O_4$: C, 61.73; H, 4.21; N, 13.50. Found: C, 61.58; H, 4.25; N, 13.64.

Reaction of Ethyl 5-Aminooxazole-4-carboxylate with *N*-Phenylmaleimide (**2a**): A solution of ethyl 5-aminooxazole-4-carboxylate (**6a**) (1.78 g, 10 mmol) and **2a** (1.73 g, 10 mmol) in 1,2-dichloroethane was refluxed for 24 h, then worked up in the manner described above to give **5a** (2.36 g, 76%).

Hydrolysis of 5a——A mixture of **5a** (0.5 g) and 10% aq. HCl (10 ml) was refluxed for 2 h. The reaction mixture was brought to pH 8.0 with 10% aq. NaOH, then shaken with Et_2O. The organic layer was separated, and the aqueous layer was acidified with 10% aq. HCl. The resulting precipitates were collected, washed with water, and dried to give 3-aminopyridine-2,4,5-tricarboxylic acid (**9**), mp 215—217 °C (lit.[4] mp 215—217 °C).

Preparation of Ethyl 3-Aminopyridine-2-carboxylates (5)——General Procedure: A solution of ethyl 2-acylamino-2-cyanoacetate (**4**), olefin (**2**) and trifluoroacetic acid in 1,2-dichloroethane was refluxed for 10—30 h. After removal of the solvent, the residue was neutralized with 5% aq. $NaHCO_3$ solution and extracted with $CHCl_3$. The extracts were washed with water, dried and concentrated to leave a solid, which was chromatographed on a silica gel column. Elution with $CHCl_3$ gave **5**: Yields and physical data are as follows.

7-Amino-6-ethoxycarbonyl-4-methyl-1,3-dioxo-2-phenyl-1,3-dihydropyrrolo[3,4-*c*]pyridine (**5b**): Yield 70%, mp 199—200 °C (needles from AcOEt). IR ν_{max}^{KBr} cm^{-1}: 1720, 1715. MS *m/e*: 325 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.47 (3H, t,

CH_3), 2.80 (3H, s, CH_3), 4.52 (2H, q, CH_2), 7.50 (5H, s, C_6H_5). *Anal.* Calcd for $C_{17}H_{15}N_3O_4$: C, 62.67; H, 4.65; N, 12.92. Found: C, 62.74; H, 4.69; N, 12.71.

Ethyl 3-Amino-4,5-dicyanopyridine-2-carboxylate (**5c**): Yield 10%, mp 139—140 °C (pale yellow needles from isopropyl ether). IR ν_{max}^{KBr} cm^{-1}: 2230, 1695. MS *m/e*: 216 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.48 (3H, t, J=7 Hz, CH_3), 4.52 (2H, q, J=7 Hz, CH_2), 8.32 (1H, s, pyridine ring proton). *Anal.* Calcd for $C_{10}H_8N_4O_2$: C, 55.55; H, 3.72; N, 25.92. Found: C, 55.84; H, 3.90; N, 25.96.

Ethyl 3-Amino-4,5-dicyano-6-methylpyridine-2-carboxylate (**5d**): Yield 10%, mp 139—140 °C (pale yellow needles from isopropyl ether). IR ν_{max}^{KBr} cm^{-1}: 2220, 1690. MS *m/e*: 230 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 2.73 (3H, s, CH_3), 6.62 (2H, br, NH_2). *Anal.* Calcd for $C_{11}H_{10}N_4O_2$: C, 57.36; H, 4.38; N, 24.32. Found: C, 57.47; H, 4.35; N, 24.35.

Ethyl 3-Amino-4-cyanopyridine-2-carboxylate (**5e**): Yield 30%. mp 118 °C (pale yellow needles from isopropyl ether). IR ν_{max}^{KBr} cm^{-1}: 2220, 1680. MS *m/e*: 205 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 6.4—6.7 (2H, br, NH_2), 7.48 (1H, d, J= 5 Hz, pyridine ring proton), 8.15 (1H, d, J=5 Hz, pyridine ring proton). *Anal.* Calcd for $C_9H_9N_3O_2$: C, 56.54; H, 4.74; N, 24.32. Found: C, 56.88; H, 4,85; N, 21.75.

Ethyl 3-Amino-4-cyano-6-methylpyridine-2-carboxylate (**5f**): Yield 35%, mp 138—139 °C (pale yellow needles from isopropyl ether). IR ν_{max}^{KBr} cm^{-1}: 2230, 1690. MS *m/e*: 205 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 2.55 (3H, s, CH_3), 7.40 (1H, s, pyridine ring proton). *Anal.* Calcd for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.37; N, 20.49. Found: C, 58.36; H, 5.62; N, 20.37.

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