Structure and Properties of Ethyl (2-Benzimidazolyl)cyanoacetimidate

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Received October 13, 1998

The revision of the structure of hydrolytic product from 4-cyano-1-ethoxypyrimido[1,6-*a*]benzimidazole (**1**) and the properties of ethyl (2-benzimidazolyl)cyanoacetimidate (**3a**) are described.

J. Heterocyclic Chem., **36**, 841 (1999).

In a previous paper, we reported that 4-cyano-1-ethoxypyrimido[1,6-*a*]benzimidazole (**1**) was hydrolyzed to ynaminonitrile derivative **2** under both acidic and basic conditions, and the structure of **2** was elucidated on the basis of its nmr spectral data (Scheme 1) [1]. To confirm the structure of **2**, we recrystallized the hydrolytic product from acetonitrile for the X-ray structural analysis. The X-ray analytical data revealed that the structure of the hydrolytic product was not **2** but ethyl (2-benzimidazolyl)cyanoacetimidate (**3a**) (Table 1, Table 2, Figure 1).

The mechanisms of the hydrolysis of **1** are proposed in Scheme 2. Under basic conditions, water attacks the carbon at the 3-position of **1** to give intermediate **4** whose pyrimidine ring was cleaved to **5** through proton shift. The aldehyde of **5** is converted to geminal diol **6**, where the proton shift, followed by the loss of formic acid provided imidate **3a**. Imidate **3a** was also formed under acidic conditions. This could also be explained by similar mechanisms where protonation first occurred on nitrogen at the 5-position of **1** (Scheme 3).

Scheme 1

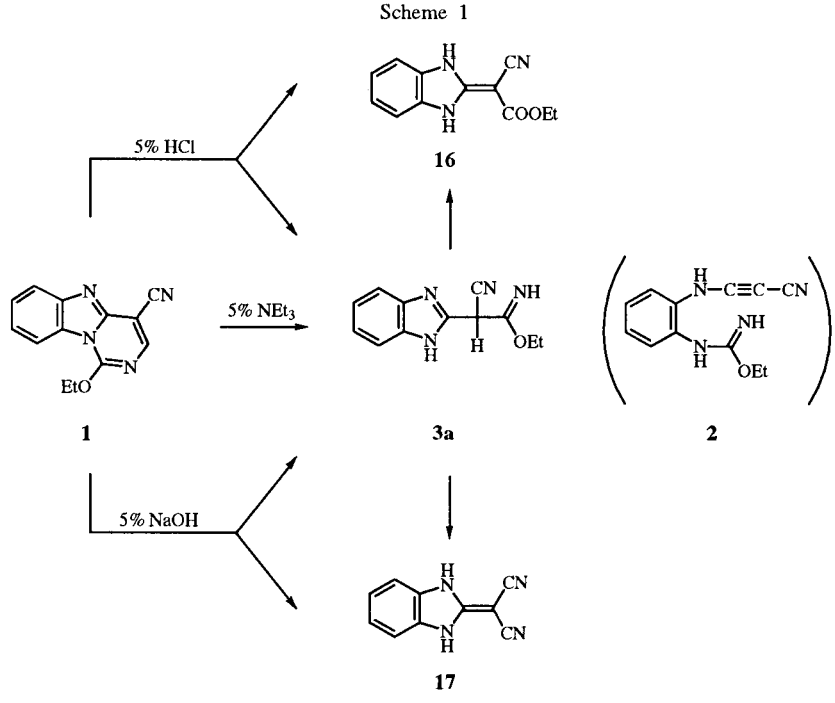


Table I

Positional Parameters and Their Estimated Standard Deviations for Compound **3a**

Atom	x	y	z	β_{eq}
O(1)	0.3900(3)	0.0365(3)	0.1988(4)	3.8(3)
N(1)	0.5640(4)	-0.1182(4)	0.4643(5)	3.4(3)
N(2)	0.4143(4)	-0.1090(4)	0.5007(5)	3.6(3)
N(3)	0.6180(4)	-0.0061(4)	0.2149(5)	4.8(4)
N(4)	0.3132(4)	-0.0206(4)	0.3534(5)	4.2(3)
N(5)	0.7346(5)	0.1266(7)	0.9239(8)	9.4(6)
C(1)	0.4170(7)	-0.1995(6)	0.6753(8)	4.7(5)
C(2)	0.4739(7)	-0.2463(6)	0.7396(8)	5.5(5)
C(3)	0.5665(7)	-0.2528(6)	0.7162(9)	5.5(6)
C(4)	0.6049(7)	-0.2120(5)	0.6260(8)	4.6(5)
C(5)	0.5480(5)	-0.1648(5)	0.5597(7)	3.8(4)
C(6)	0.4555(5)	-0.1589(5)	0.5829(7)	3.9(4)
C(7)	0.4822(5)	-0.0861(5)	0.4324(7)	3.5(4)
C(8)	0.4729(5)	-0.0339(5)	0.3337(6)	3.2(4)
C(9)	0.5531(5)	-0.0177(5)	0.2659(7)	3.6(4)
C(10)	0.3879(5)	-0.0062(5)	0.2964(7)	3.5(4)
C(11)	0.3062(5)	0.0750(5)	0.1623(6)	4.0(4)
C(12)	0.3296(5)	0.1252(5)	0.0591(7)	5.1(5)
C(13)	0.5697(6)	0.1219(6)	0.9916(3)	6.1(6)
C(14)	0.6636(7)	0.1236(7)	0.9545(8)	6.1(6)

Table II

Selected Bond Lengths and Bond Angles of **3a**

Bond Length (Å)		Bond Angle (°)	
O(1)-C(10)	1.339 (8)	O(1)-C(10)-N(4)	122.9 (7)
N(1)-C(5)	1.377 (9)	N(1)-C(7)-N(2)	112.6 (7)
N(1)-C(7)	1.373 (8)	N(2)-C(6)-C(5)	109.7 (7)
N(2)-C(6)	1.409 (9)	N(2)-C(7)-C(8)	122.5 (7)
N(2)-C(7)	1.330 (9)	N(3)-C(9)-C(8)	177.9 (9)
N(3)-C(9)	1.139 (9)	N(4)-C(10)-C(8)	122.3 (7)
N(4)-C(10)	1.305 (9)	C(5)-N(1)-C(7)	107.1 (6)
C(7)-C(8)	1.45 (1)	C(6)-N(2)-C(7)	104.5 (6)
C(8)-C(9)	1.44 (1)	C(7)-C(8)-C(9)	117.6 (7)
C(8)-C(10)	1.405 (9)	C(10)-O(1)-C(11)	117.9 (6)

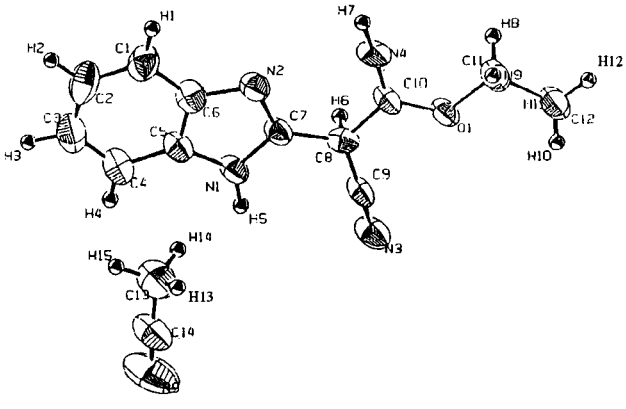


Figure 1. X-ray structure of **3a** with acetonitrile showing crystallographic numbering scheme.

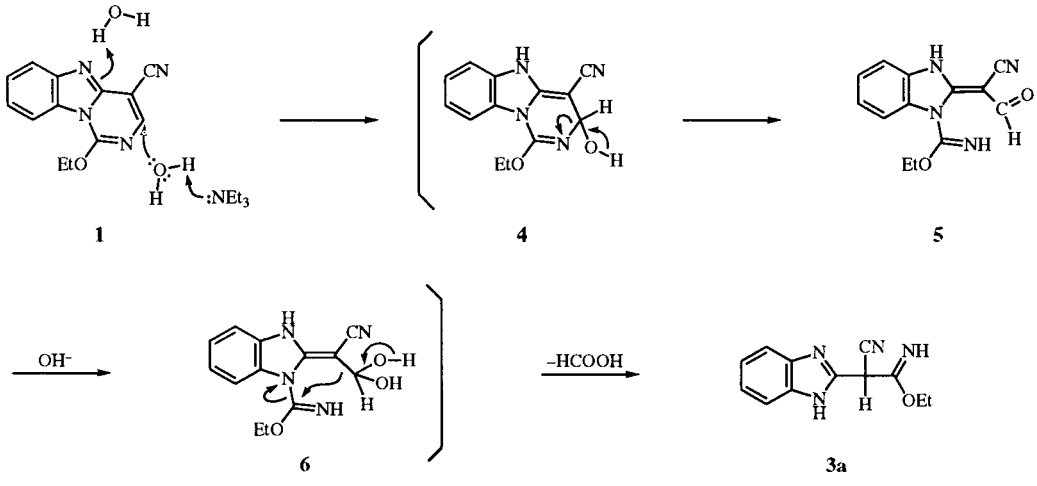
Although free imidates, in general, are very susceptible to hydrolysis, imidate **3a** is surprisingly stable. This might be due to a tautomerism among enamine type **3b**, imidate **3a**, and azadiene type **3c** as shown in Scheme 4. Also, imidate **3a** itself is able to have an optical isomer, and this kind of tautomerism of **3a** has already been studied by nmr methods (Scheme 5). Töke and co-workers indicated that the ratio of imine type **11a** and **11c** to enamine type **11b** of an indole alkaloid was 85/15 in deuteriodimethyl sulfoxide solution [2]. Ahlbrecht and Vonderheid also reported the tautomerism of ethyl cyanoacetimidate where imidate type **12b** and enamine types **12a** and **12c** were present in deuteriodimethyl sulfoxide [3]. We also attempted to analyze the tautomerism of the imidate **3a** by the nmr method in deuteriodimethyl sulfoxide solution. The pmr spectra showed three broad signals at 8.60, 10.43 and 11.85 ppm which might be due to three NH protons. The ^{13}C nmr spectra showed a quaternary carbon signal at 54.1 ppm, but a methine carbon signal for **3a** could not be observed. These facts indicate that there would exist a rapid proton exchange through the tautomers.

In general, imidate **13** is hydrolyzed to ester **14** or amide **15** under acidic or basic conditions, respectively (Scheme 6) [4]. Since the reason why compound **1** was hydrolyzed in 5% hydrochloric acid to 2-(cyanoethoxycarbonyl)methylenebenzimidazoline (**16**) in 25% yield along with **3a** (57%), and why **1** was hydrolyzed in 5% sodium hydroxide solution to 2-dicyanomethylenebenzimidazoline (**17**) in 79% yield along with **3a** (6%) was found to be the results of the hydrolysis of imidate **3a** which was formed from **1**. It is worth noting that the hydrolysis of **3a** did not afford (2-benzimidazolyl)cyanoacetamide (**23**) under basic conditions (See also Scheme 1). We proposed a mechanism producing **17** in Scheme 7 where the active methine proton was withdrawn from imidate **3a** to give carbanion **18**, then electron transfer and its push-pull mechanism of intermediate **19** afforded tautomer **20** which isomerized to **17** as a crystalline substance.

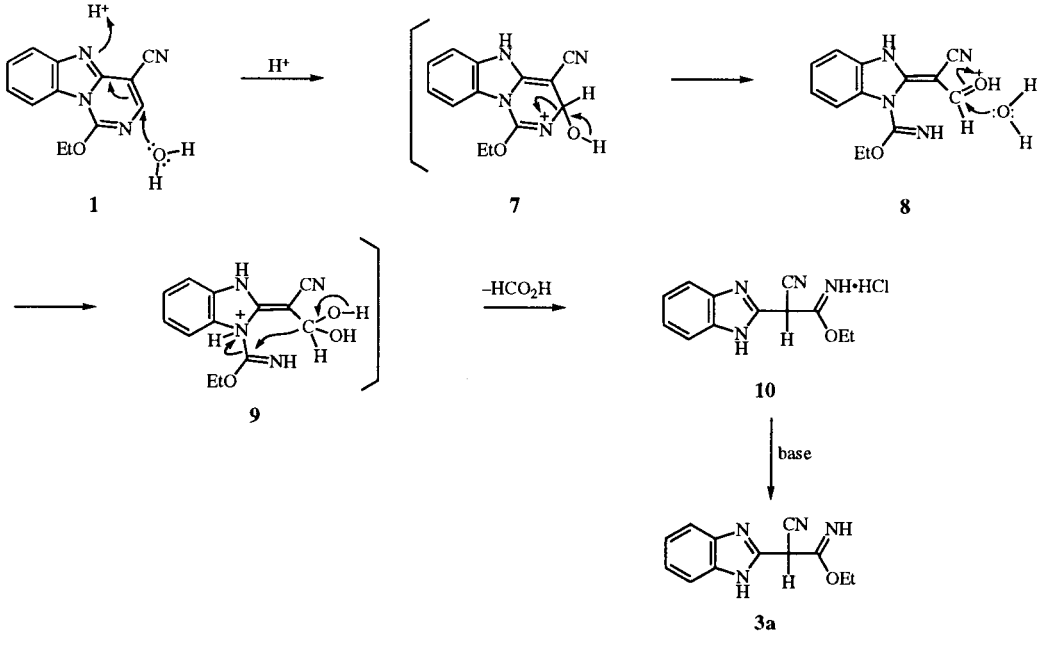
On thermal decomposition of imidates, most of unsubstituted imidate hydrochlorides **21** do not have true melting points but rather leaving a residual amide **22** (Scheme 8) [5]. As shown in Scheme 9, when imidate **3a** was refluxed in acetic acid, (2-benzimidazolyl)cyanoacetamide (**23**) was obtained. To clarify the reaction mechanisms, imidate **3a** was refluxed in acetic acid containing ^{18}O-labeled water. If imidate **3a** reacts with water, intermediate **24** must be formed, and the intermediate **24** must give ^{18}O-labeled amide **26** by the elimination of ethanol. However, the expected amide **26** was not obtained but only **23**. These results indicate that intermediate **25** is more stable than **24**.

Imidate **3a** reacted with amines as usual. When excess primary amines were allowed to react with **3a**, *N*-substi-

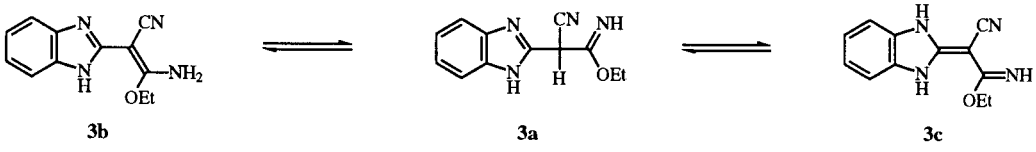
Scheme 2



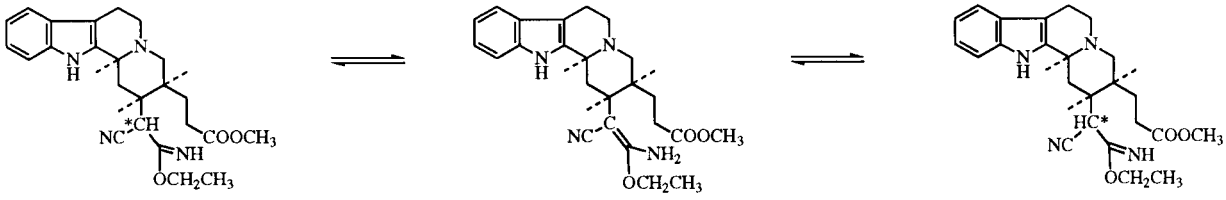
Scheme 3



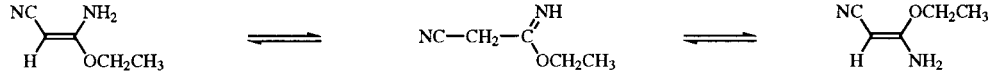
Scheme 4



Scheme 5

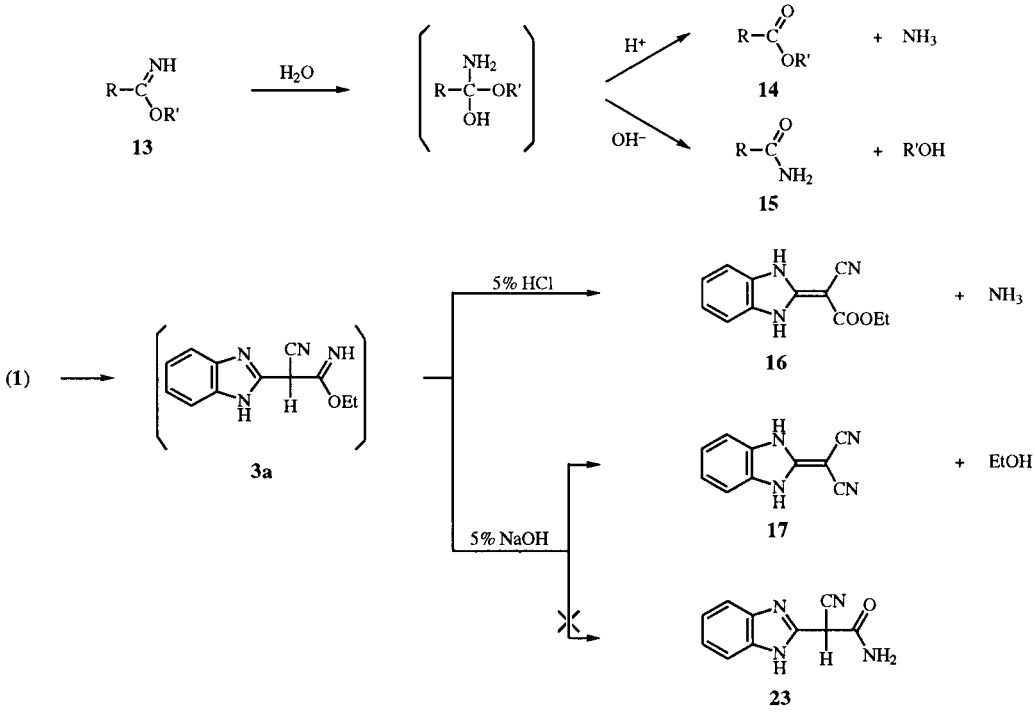


Imine Type **11a** | Enamine Type **11b** | Imine Type **11c**

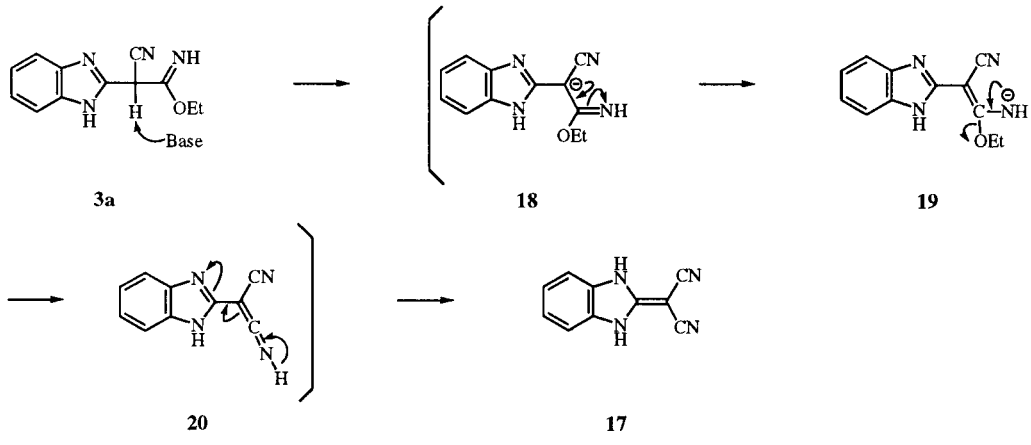


Enamine Type **12a** | Imidate Type **12b** | Enamine Type **12c**

Scheme 6

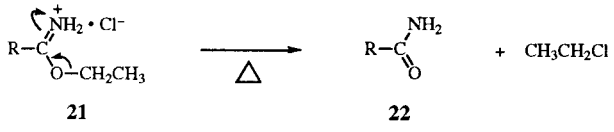


Scheme 7

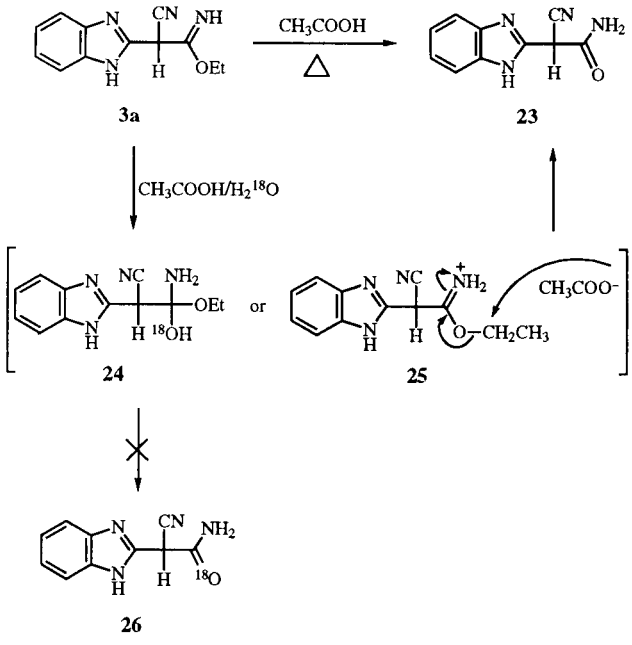


tuted amidine **27** and *N,N'*-disubstituted amidine **28** were obtained (Scheme 10). The reaction of **3a** with hydrazine hydrate and ethylenediamine gave 3,5-diamino-4-(2-benzimidazolyl)pyrazole (**29**) and 2-(2-benzimidazolyl)-2-(2-imidazolinyl)ethanenitrile (**30**), respectively (Scheme 10).

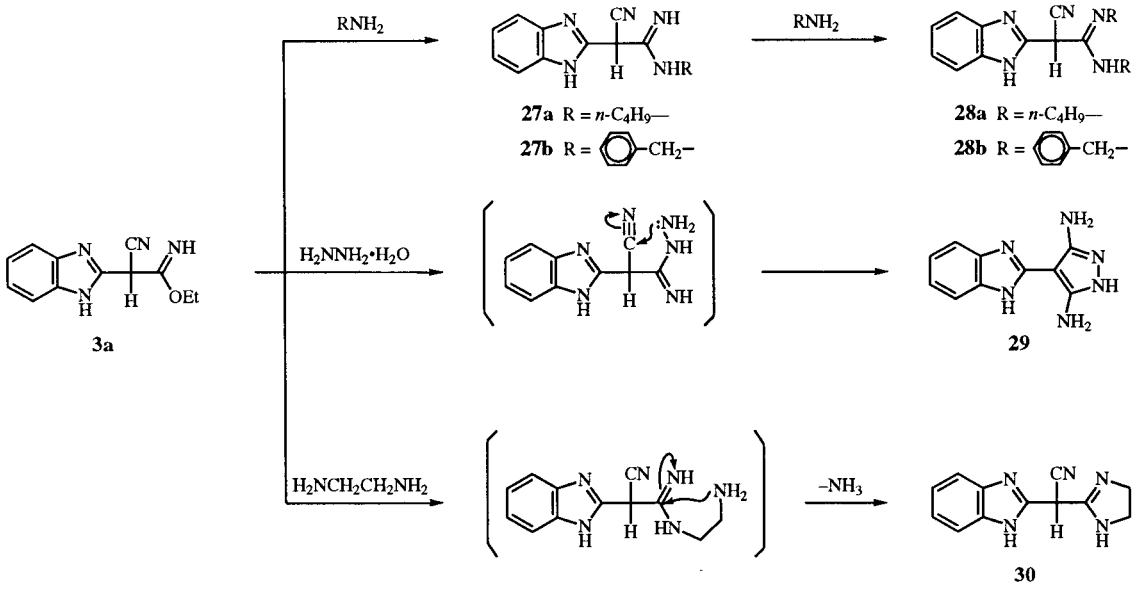
Scheme 8



Scheme 9



Scheme 10



EXPERIMENTAL

All melting points were determined on a Yazawa micro melting point BY-2 apparatus and are uncorrected. The ir spectra (potassium bromide) were recorded with a JASCO IRA-1 spectrophotometer. The nmr spectra were measured in deuteriodimethyl sulfoxide with a VXR-300 spectrometer at 300 MHz. The mass spectra (ms) were determined with a JEOL O1S spectrometer. Elemental analyses were performed on a Perkin-Elmer 240B instrument.

X-Ray Structural Analysis of **3a**.

A crystal was mounted on a Rigaku AFC-5R diffractometer, and the cell parameters and the intensity data measured with graphite-monochromated CuKα (λ = 1.54179Å) radiation at 23°. Approximate atomic coordinates were obtained by the direct method using MITHRIL [7]. The parameters of non-hydrogen atoms were refined by the full-matrix least-squares method with anisotropic temperature factors. The hydrogen atoms were located from a difference Fourier synthesis, and refined with isotropic temperature factors. The crystal data are as follows: Chemical formula $C_{12}H_{12}N_4O$; MW 228.25; orthorhombic; space group *Pbca*; Z = 8; unit cell dimensions a = 14.722(3) Å, b = 17.078(4) Å, c = 11.500(4) Å, V = 2891(1) Å^3; 3Dcal = 1.049 gcm^{-3}; μ (CuKα) = 5.46 cm^{-1}; crystal size 0.4 x 0.1 x 0.1 mm. Of the total of 2889 reflections up to the 2θ range of 140.2°, 1297 were measured as above the 3σ (I) level and were used. The final R value was 0.083. The positional parameters for **3a** are listed in Table I. The selected bond lengths and bond angles for **3a** are listed in Table II.

Ethyl (2-Benzimidazolyl)cyanoacetimidate **3a**.

A suspension of **1** (0.1 g, 0.42 mmole) in 20 ml of 5% aqueous triethylamine solution was heated in a water bath for 1 hour. After having been cooled, the precipitate was collected by suction filtration, washed with water and dried to yield pure **3a** in 70% yield (68 mg), mp 203-204°; ir: 2200 cm^{-1} (C≡N); pmr: 1.35 (3H, t, CH_3), 4.31 (2H, q, CH_2), 7.02-7.08 (2H, m, aromatic), 7.33 and 7.42 (1H, d, aromatic, respectively), ^{13}C nmr: 14.3, 54.1, 65.1, 110.5, 116.1, 119.0, 120.7, 121.0, 133.7, 142.7, 151.8, 168.6; ms: m/z 228 (M^+).

Anal. Calcd. for $C_{12}H_{12}N_4O$: C, 63.15; H, 5.30; N, 24.55. Found: C, 63.13; H, 5.23, N, 24.22.

Hydrolysis of **1** with 5% Hydrochloric Acid.

A solution of **1** (0.1 g, 0.42 mmole) in 20 ml of 5% hydrochloric acid was heated on a water bath for 1 hour to precipitate colorless needles of **16** in 25% yield (24 mg). The analytical data of **16** coincided with those of the authentic sample [6].

The filtrate was neutralized with 5% sodium bicarbonate solution to yield a precipitate of colorless crystals of **3a** (36 mg), and after filtration of **3a**, the filtrate was extracted with chloroform (50 ml, 3 times). The extract was evaporated under reduced pressure to give additional crystals of **3a** (19 mg), total yield, 57%.

Hydrolysis of **1** with 5% Sodium Hydroxide Solution.

A suspension of **1** (0.1 g, 0.42 mmole) in 20 ml of 5% sodium hydroxide solution was heated at 80° on a water bath for 1 hour. After having been cooled, the solution was neutralized (*p*H 6.5-7.0) by addition of diluted hydrochloric acid. The crystalline precipitate was collected by suction filtration, washed with water, and recrystallized from ethanol to give **17** (60 mg, 79%), which was identified by comparison of its ir and nmr spectra with those of an authentic sample [6].

From the filtrate, colorless crystals of **3a** (6 mg, 6%) were obtained.

(2-Benzimidazolyl)cyanoacetamide **23**.

Water (H_2O or $H_2{}^{18}O$) 0.02 g, 1.1 mmoles) was added to a solution of **3a** (0.1 g, 0.43 mmole) in 10 ml of acetic acid. The mixture was refluxed for 3 hours, and the solvent was evaporated under reduced pressure to give crystals. The crystals were washed with dichloromethane to provide an analytically pure

sample of **23**, mp 277-278°; ir: 2190 cm^{-1} (C≡N), 1620 cm^{-1} (C=O); pmr: 6.40 (2H, s, amide), 7.10 (2H, q, aromatic), 7.35 (2H, b, aromatic), 12.15 (2H, b, imidazoline NH); ^{13}C nmr: 51.6, 111.0, 120.8, 122.3, 130.9, 153.4, 168.9; ms: m/z 200 (M^+).

Anal. Calcd. for $C_{10}H_8N_4O$: C, 60.00; H, 4.03; N, 27.99. Found: C, 59.78; H, 4.24; N, 27.71.

Reaction of Ethyl (2-Benzimidazolyl)cyanoacetimidate with Amines.

General Procedure.

The amine (for example, butyl amine 10 g, 0.14 mole) was added to **3a** (0.1 g, 0.43 mmole) and the mixture was refluxed for 2 hours, then the solution was evaporated to provide an oily substance. The substance was chromatographed on silica gel column using chloroform as the eluant to afford a *N*-substituted amidine and a *N,N'*-disubstituted amidine.

(2-Benzimidazolyl)cyano-*N*-butylacetamidine **27a**.

This compound had mp 155-157°, 0.033 g; ms: m/z 255 (M^+).

Anal. Calcd. for $C_{14}H_{17}N_5$: C, 65.86; H, 6.71; N, 27.43. Found: C, 65.59; H, 6.69; N, 27.21.

(2-Benzimidazolyl)cyano-*N,N'*-dibutylacetamidine **28a**.

This compound had mp 143-144°, 0.005 g; ms: 311 (M^+).

Anal. Calcd. for $C_{18}H_{25}N_5$ C, 69.42; H, 8.09; N, 22.49. Found: C, 69.28; H, 8.08; N, 22.27.

(2-Benzimidazolyl)cyano-*N*-benzylacetamidine **27b**.

This compound had mp 119-120°, 0.051 g; ms: m/z 289 (M^+).

Anal. Calcd. for $C_{17}H_{15}N_5$: C, 70.57; H, 5.23; N, 24.20. Found: C, 70.68; H, 5.42; N, 23.98.

(2-Benzimidazolyl)cyano-*N,N'*-dibenzylacetamidine **28b**.

This compound had mp 178-180°, 0.016 g; ms: m/z 379 (M^+).

Anal. Calcd. for $C_{24}H_{21}N_5$: C, 75.97; H, 5.58; N, 18.46. Found: C, 75.81; H, 5.74; N, 18.34.

3,5-Diamino-4-(2-benzimidazolyl)pyrazole **29**.

Hydrazine hydrate (0.8 g, 0.016 mole) was added to a solution of **3a** (0.1 g, 0.43 mmole) in 10 ml of ethanol and the mixture was refluxed on a water bath for 2 hours. After having been cooled, the precipitate was filtered by suction filtration, washed with ethanol, and dried under reduced pressure to give analytically pure crystals of **29** in 73% yield (0.069 g), mp >300°; pmr: 5.40 (2H, b, NH_2), 5.80 (2H, b, NH_2), 7.03 (2H, m, aromatic), 7.40 (2H, b, aromatic), 10.65 (1H, b, NH), 11.46 (1H, b, NH); ms: m/z 214 (M^+).

Anal. Calcd. for $C_{10}H_{10}N_6$: C, 56.07; H, 4.70; N, 39.23. Found: C, 55.98; H, 4.81; N, 39.12.

2-(2-Benzimidazolyl)-2-(2-imidazolinyl)ethanenitrile **30**.

A solution of **3a** (0.1 g, 0.43 mmole) and ethylenediamine (1 g, 0.017 mole) in 10 ml of butanol was refluxed for 2 hours. The solution was evaporated under reduced pressure to provide an oily substance which was chromatographed on a silica gel column using chloroform as eluant. The crystals of **30** were obtained in 23% yield (0.023 g), mp 285-287°; ms: m/z 225 (M^+).

Anal. Calcd. for $C_{12}H_{11}N_5$: C, 63.99; H, 4.92; N, 31.09. Found: C, 63.87; H, 4.88; N, 31.18.

REFERENCES AND NOTES

[1] Y. Zama, Y. Okamoto, K. Takagi, Y. Kurasawa and A. Takada, *J. Heterocyclic Chem.*, **32**, 851 (1995).

[2] L. Töke, G. Blasko, L. Szabo and Cs. Szantay, *Tetrahedron Letters*, 2459 (1972).

[3] H. Ahlbrecht and C. Vonderheid, *Chem. Ber.*, **106**, 2009 (1973).

[4] D. G. Neilson, The Chemistry of Amidines and Imidates, S. Patai, ed, John Wiley & Sons, New York, pp 422-423 (1975) and literatures cited therein.

[5] R. Roger and D. G. Neilson, *Chem. Rev.*, **61**, 179 (1961).

[6] Y. Okamoto, K. Takagi, A. Takada and T. Ueda, *J. Org. Chem.*, **49**, 908 (1984).

[7] C. J. Gilmore: MITHRIL an integrated direct method computer program, Univ. of Glasgow, Scotland, *J. Appl. Cryst.*, **17**, 42 (1984).