Hydrolysis of 4-Cyano-1-ethoxypyrimido[1,6-*a*]benzimidazole: Formation of a Ynaminonitrile and Benzimidazolidines

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The title compound **4** was hydrolyzed to a new type of ynaminonitrile **5** and benzimidazolidines **7** and **9** under acidic or basic conditions. Reaction mechanisms were proposed.

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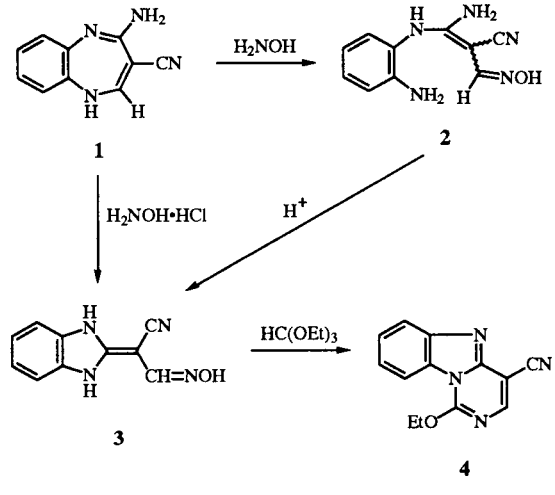
In a previous paper [1], we synthesized 4-cyano-1-ethoxypyrimido[1,6-*a*]benzimidazole **4** by the reaction of ethyl orthoformate with 3-amino-3-(2-aminoanilino)-2-cyanopropenal oxime **2** which was readily obtained *via* a ring opening reaction of 4-amino-1*H*-1,5-benzodiazepine-3-carbonitrile **1** with hydroxylamine. Compound **4** seems to have an interesting structure because it possesses an iminoether moiety in the molecule where the functional group can probably be activated for the nucleophilic reaction due to both the cyano group at the 4 position and 5-aza-3,4a-diene moiety of **4**. In general, an iminoether group is readily hydrolyzed, so that we tried hydrolyses of **4**. In the formation of **4** from **2** and ethyl orthoformate, 2-(2-benzimidazolidinylidene)-2-cyanoethanal oxime **3** was thought to be an intermediate which would be formed by removal of ammonia from **2** [1]. In fact, compound **4** was found to be prepared in a better yield by refluxing of **3** in ethyl orthoformate. Compound **3** was readily obtained by treatment of **2** with diluted hydrochloric acid (Scheme 1).

Scheme 1

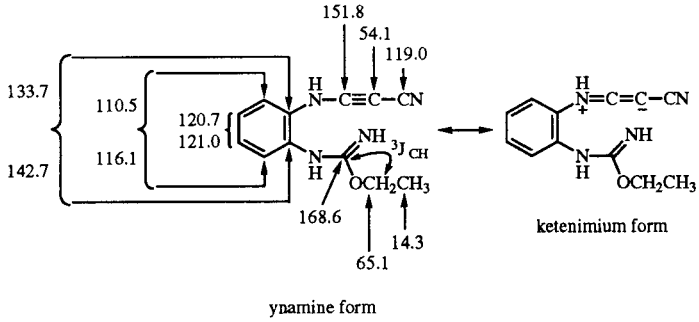


Hydrolysis under Basic Conditions.

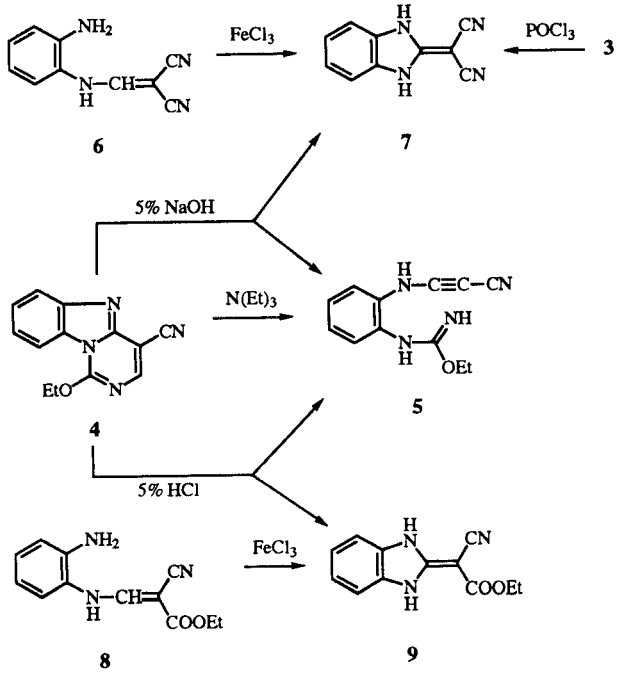
Compound **4** was hydrolyzed in the presence of triethylamine to give [2-(ethoxyiminomethylamino)anilino]ethynecarbonitrile **5** in 70% yield (Scheme 2). The structure of **5** was based on elementary analyses and spectral data. Especially, the long-range $^1H/^{13}C$ COSY spectra established each of the chemical shifts of ^{13}C as shown in Chart 1. It is worth noting that one of acetylenic carbon signals appeared at 151.8 ppm which was at an extraordinarily lower field. This might be due to resonance-stabilization between the ynamine form and the keteniminium form of compound **5** [2]. However, when **4** was heated in 5% sodium hydroxide solution at 80° for 1 hour, pale yellow crystals of 2-(dicyanomethylene)benzimidazolidine **7** were obtained in 78% yield in addition to **5** in 2% yield. The structure **7** was finally confirmed by two authentic syntheses, oxidative cyclization of 2-[(2,2-dicyanovinyl)amino]aniline **6** with ferric chloride [3], and dehydration of the aldoxime **3** with phosphorus oxychloride. The above results indicate that **4** undergoes two different degradations depending on the basicity of the base used.

A possible mechanism for the formation of **5** is shown in Scheme 3. Water as nucleophile attacks at 3 position of **4** to cause N^2-C^3 bond cleavage through general acid and base catalysis [4], and the resulting aldehyde **11** might be

Chart 1



Scheme 2



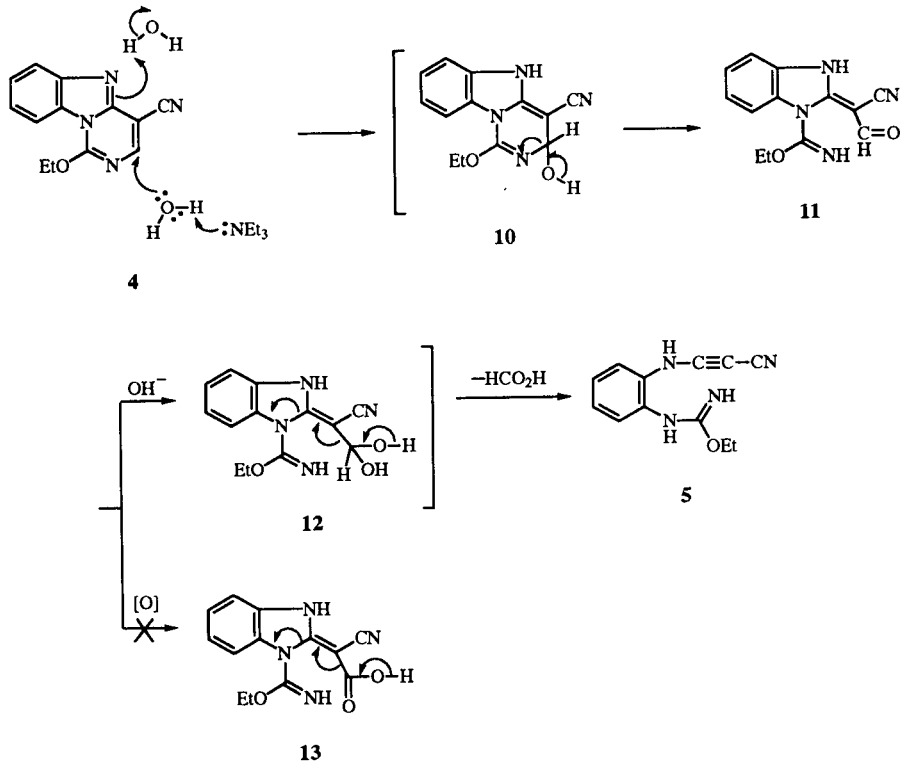
hydrated to a gem-diol **12** or oxidized to a carboxylic acid **13** which provides **5** through loss of formic acid or decarboxylation, respectively. To confirm whether oxygen involved in the reaction or not, we attempted to hydrolyze **4** under nitrogen stream, and obtained **5** in a similar yield described above. Therefore, compound **4** was hydrolyzed to **5** through intermediates **10**, **11**, and **12**. On the other hand, the formation of **7** from **4** can be explained by initial attack of hydroxide anions at the 1 position of **4**, followed by C^1-N^{10} bond fission to give a urethan **15** which tautomerizes, and is hydrolyzed, followed by dehydrogenation with decarboxylation to **7** (Scheme 4). Since compound **7** was obtained from **4** in a similar yield under nitrogen stream, oxygen did not involve in the reaction.

Hydrolysis under Acidic Conditions.

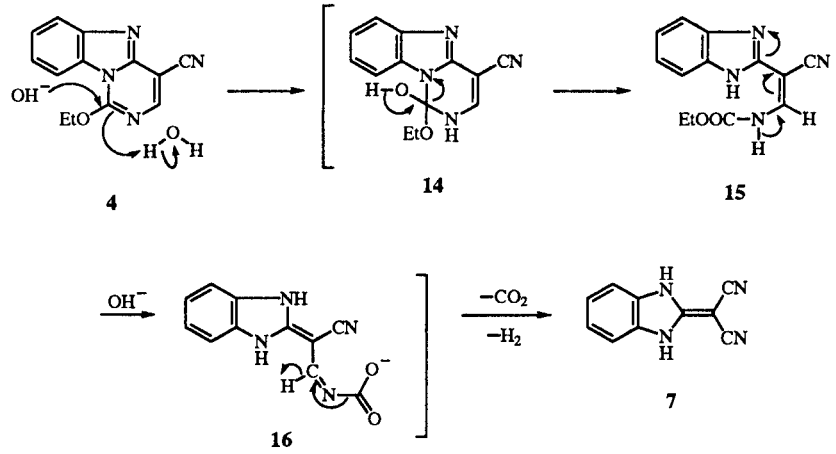
In contrast, we examined the behavior of **4** in acidic media. When **4** was heated in 5% hydrochloric acid under conditions of both air and nitrogen, compounds **5** and 2-(carbethoxycyanomethylene)benzimidazolidine **9** were obtained in 56% and 25% yields, respectively (Scheme 2). The structure of **9** was supported by an unequivocal synthesis constituting of the oxidative cyclization of 2-[(2-cyano-2-carbethoxyvinyl)amino]aniline **8** with ferric chloride [3]. It is worth noting that no reaction was observed when compound **4** was heated in 5% aqueous solution of acetic acid.

We proposed plausible mechanisms for the formation of **5** and **9** in Scheme 5 and 6, respectively. When proto-

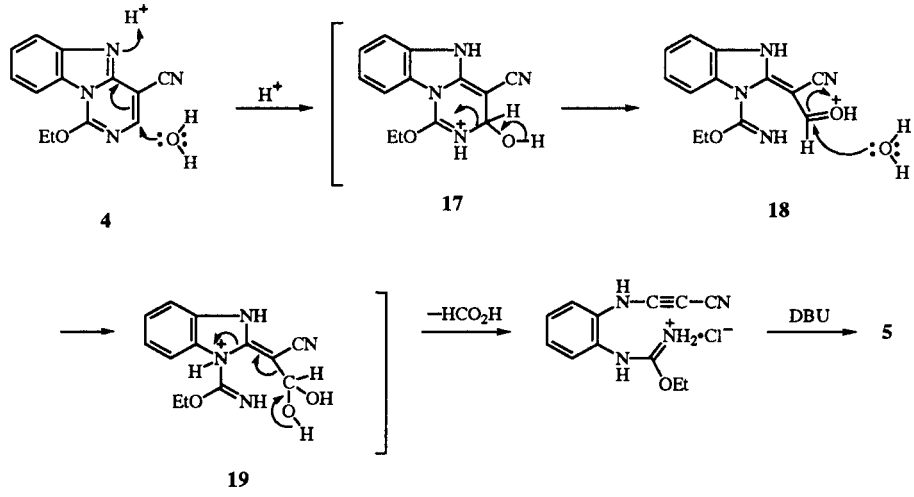
Scheme 3



Scheme 4



Scheme 5



nation occurs at the 5 position in compound **4**, water attacks at the 3 position to give **17**, whose ring opening provides an aldehyde **18**. The carbonyl group of **18** is hydrated to **19** from which loss of formic acid provides the hydrochloride of **5** (Scheme 5). The mechanism of the hydration might be explained in terms of a general acid and base catalysis, or a simultaneous proton transfer and attack of water as a nucleophile [4]. When protonation occurs at the 2 position in compound **4**, water attacks at the 1 position to give **20**, whose ring opening provides urethan **21**. The proton transfer of **21** gives **22** which cyclizes to **23** intramolecularly. The ring opening of **23** through the proton transfer gives **24** with 1,3-migration of the ester group. This kind of migration was reported previously [5]. Hydrolysis of the imino group of **24** affords an aldehyde **25** from which loss of formic acid provides **9**.

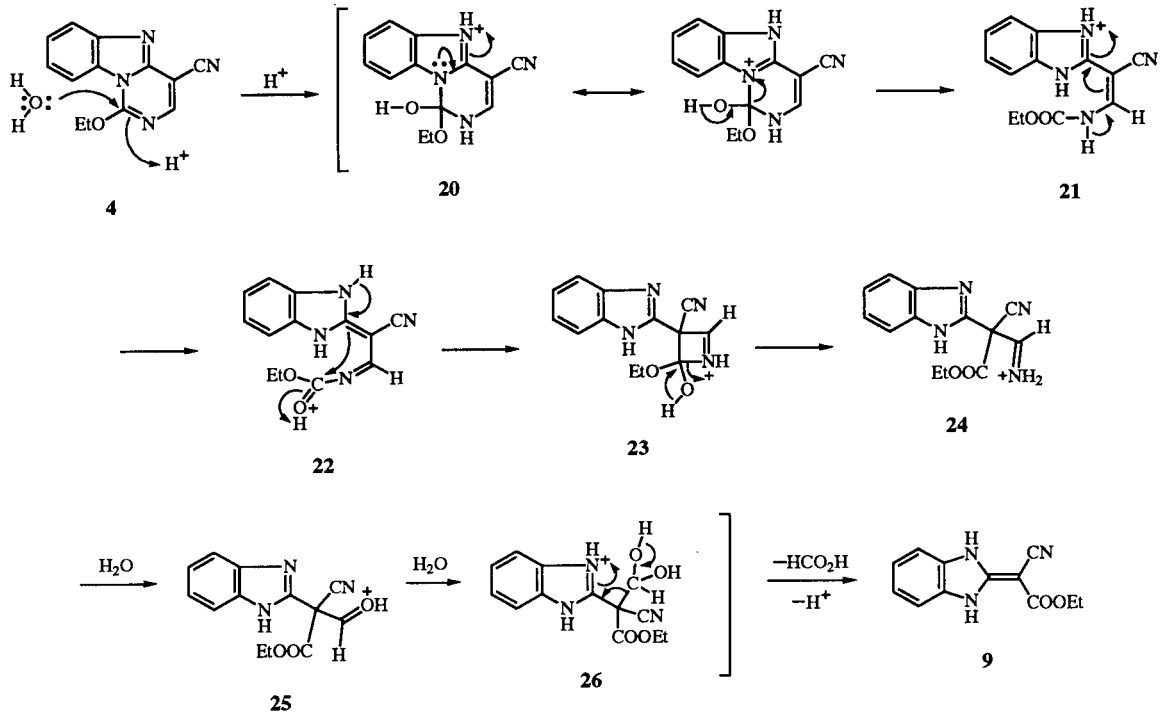
EXPERIMENTAL

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 (ms) spectra were determined with a JEOL O1S spectrometer. Elemental analyses were performed on a Perkin-Elmer 240B instrument.

2-(2-Benzimidazolidinylidene)-2-cyanoethanal Oxime **3**.

a) A mixture of 1 g (4.5 mmoles) of the hydrochloride salt of **1** and 0.5 g (14.4 mmoles) of hydroxylamine hydrochloride in 50 ml of water was heated on a water bath for 5 hours to provide almost pure crystals of **3** in 93% yield (0.85 g). Recrystallization from ethanol gave prisms of **3**, mp 263° dec; ir: cm^{-1} 2190 (C≡N); pmr: 6.32 (1H, s, NH), 7.00-7.60 (5H, m, aromatic), 12.17 (2H, s, NH_2); ms: m/z 200 (M^+).

Scheme 6



Anal. Calcd. for $C_{10}H_8N_4O$: C, 59.99; H, 4.02; N, 27.99. Found: C, 59.71; H, 4.11; N, 27.83.

b) A suspension of 1 g of **2** in 50 ml of water was treated with 1 ml of 10% hydrochloric acid at room temperature. After 20 minutes needles of **4** (0.89 g, 98%) precipitated.

4-Cyano-1-ethoxypyrimido[1,6-*a*]benzimidazole **4**.

A suspension of **3** (0.32 g, 1.6 mmoles) in ethyl orthoformate (60 ml, 0.36 mole) was refluxed for 3.5 hours. After removal of the excess of ethyl orthoformate under reduced pressure, the residue was recrystallized from methanol/chloroform to yield **4** (0.27 g, 50%), mp 232-233°, which was identified by comparison of its ir and nmr spectra with those of the authentic sample [1].

[2-(Ethoxyiminomethylamino)anilino]ethynecarbonitrile **5**.

A suspension of **4** (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 precipitates were collected by suction filtration, washed with water and dried to yield pure of **5** in 70% yield (68 mg), mp 203-204°; ir: 2200 cm^{-1} (C≡N); ^1H nmr: 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), 8.60, 10.43, and 11.85 (1H, b, NH, 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 **4** with 5% Sodium Hydroxide Solution.

A suspension of **4** (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 precipitates were collected by suction filtration, washed with water, and recrystallized from ethanol to give **7** (60 mg, 79%), which was identified by comparison of its ir and nmr spectra with those of the authentic sample [3].

From the filtrate, colorless crystals of **5** (6 mg, 6%) were obtained.

2-(Dicyanomethylene)benzimidazolidine **7**.

A suspension of **3** (0.2 g, 1 mmole) in 10 ml of phosphorus oxychloride was refluxed for 5 hours. The solvent was evaporated under reduced pressure to provide an oily substance which was treated with water to give **7** in 99% yield (0.18 g).

Hydrolysis of **4** with 5% Hydrochloric Acid.

A solution of **4** (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 **9** in 25% yield (24 mg). The analytical data of **9** coincided with those of the authentic sample [3].

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

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