# Synthesis and Degradation of 3-Amino-3-(2-substituted benzimidazol-1-yl)-2-(2-phenyl-1,1-diazanediylmethyl)-2-propenenitrile: Hydroxyl Group-Promoted C-N Bond Fission [1]



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The reaction of 3-amino-3-(*o*-aminoanilino)-2-cyano-2-propenal phenylhydrazone (**2**) with orthoesters gave the title compound (**3**), which was readily converted to 2-substituted benzimidazole (**4**) and 5-amino-4-cyano-1-phenylpyrazole (**5**) when heated in 1-butanol. The degradation mechanisms were proposed.

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In a series of studying ring transformations of 4-amino-1*H*-1,5-benzodiazepine-3-carbonitrile (**1**), we have reported a synthesis of ring-opened hydrazine adduct **2** [3]. This multifunctional intermediate **2** was reacted with orthoesters in order to examine its way of cyclization. This paper describes the orientations of the reactions and the degradation of the reaction products **3** which is particularly promoted by protic solvents.

As Chart 1 shows, there are at least four possible routes (i, ii, iii and iv) in the reaction of **2** with orthoester. When **2** was heated with excess amounts (2 to 8 times equivalent concentrations) of triethyl orthoformate in benzene, 3-amino-3-(benzimidazol-1-yl)-2-(2-phenyl-1,1-diazanediylmethyl)-2-propenenitrile (**3a**) was obtained in 67% yield. Similarly, **3b** and **3c** were obtained in good yields from the reactions of **2** with triethyl orthoacetate and triethyl orthopropionate, respectively, using benzene as a solvent. These results are due to the route i. In contrast, when 1-butanol was used as a solvent in the above reaction, 2-substituted benzimidazole **4** and 5-amino-4-cyano-1-phenylpyrazole (**5**) [4] were quantitatively obtained, but not any compound **3**. These products were coincided with their authentic samples in the spectral data. Analysis of **3** by the pmr spectroscopy revealed that it consisted of two isomers, namely *E* and *Z* forms whose ratio (*E*/*Z*) was about **5**. Signals of amino protons of **3** in the *Z* form were observed in the higher fields than those in the *E* form (s-*cis*) which might be formed by a hydrogen bond.

We studied on the degradation of **3c** which was heated in several solvents, and the results were summarized in Table I. All the organic solvents used were in ordinary grade but not anhydrous ones. Apparently, 1-butanol and water effectively cleaved the $C_3$-N bond of **3c**. However, when ethanol was used as a solvent, almost all of the starting material were recovered. When aprotic solvents such as pyridine and xylene were used, the total yield of the degradation products of **3c** was about a half of that obtained in 1-butanol. *N*,*N*-Dimethylformamide (DMF) as a solvent was also effective to cleave the $C_3$-N bond like 1-butanol. One of reasons might be ascribed to a trace of water contained in DMF which catalyzed the degradation reaction. In fact, the DMF effectively hydrolyzed the ester group of 8(7*H*,9*H*)-(carbethoxycyanomethylene)theophylline [5]. These results indicate that the degradation of **3** would be brought about effectively using protic solvents and at enough reaction temperature.

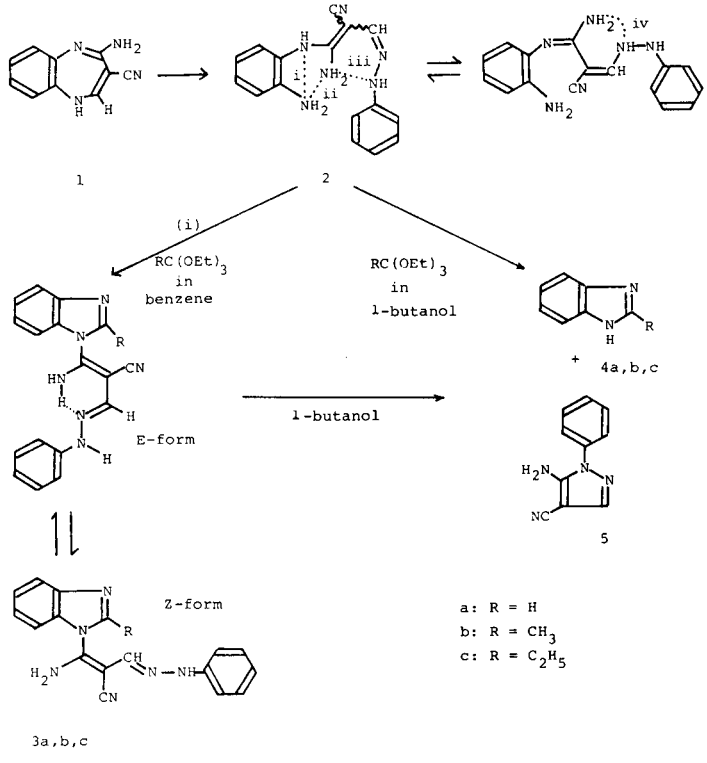


Chart 1

It is demonstrated that the degradation of **3** is an elimination, yielding **4** and **5** as the sole products. Namely, the reaction consists of two units, one is an intramolecular cyclization between nitrile and hydrazino groups, another is the $C_3$-N bond fission. Therefore, the degradation may proceed *via* an intermediate **6** which could not be isolated. As Chart 2 shows, the alcohol may interact with both im-

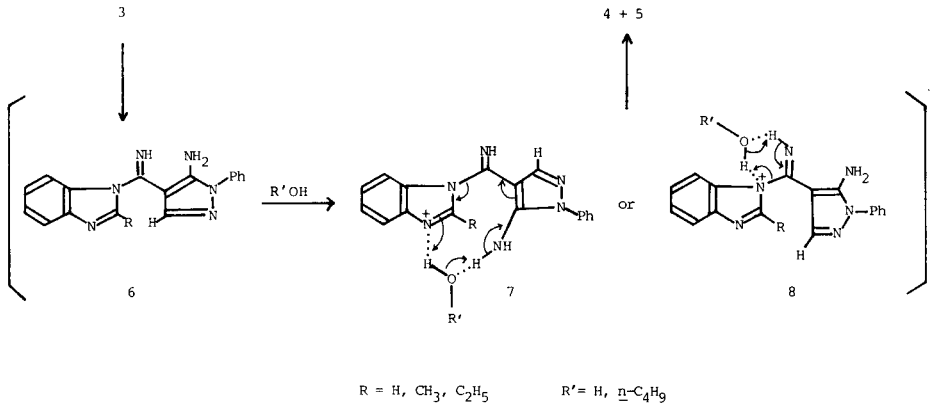


Chart 2

Table I

Conversion of **3c** into **4c** and **5**

| Solvent | Refluxing Time hours | Total Yield (%) (**4c** + **5**) |
|---|---|---|
| 1-Butanol | 5 | 100 |
| Water | 7 | 100 |
| DMF | 2.5 | 100 |
| Ethanol | 7 | ~1 [a] |
| Pyridine | 5 | 50 [a] |
| Xylene | 2.5 | 54 [a] |

[a] The balance is only the starting material.

idazole ring and imino group of **6** through hydrogen bonds to form partially polarized intermediates (**7**) and/or **8** in which electron transfer readily occurs to give **4** and **5** by the charge-relay system. Namely, this degradation would be thought as a concerted one [6]. This kind of mechanism was reported in nonenzymatic degradation of urea in aqueous media [7]. Also it may be said that the participation of the alcohol and the imidazole ring on the $C_3$-N bond fission of **3** could be similar to that of serine and histidine residues in chymotrypsin where they transfer protons by push-pull mechanism [8].

In conclusion, the reaction of **2** with orthoesters gave the title compound **3** which was readily decomposed to **4** and **5** when heated in a protic solvent at above 100°. This degradation reaction seems to be much of interest in view of general acid and base catalyzed reactions [12].

## EXPERIMENTAL

Melting points were determined by using a Yamato Scientific stirred liquid apparatus and are uncorrected. Infrared (ir) and proton magnetic resonance (pmr) spectra (deuteriodimethylsulfoxide solution, tetramethylsilane as internal standard) were recorded on a JASCO IR-G and a Varian EM-90 spectrometers, respectively. The mass (ms) spectra were run on a JEOL 01S spectrometer. Elementary analyses were performed on a Perkin-Elmer 240B instrument.

3-Amino-3-(benzimidazol-1-yl)-2-(2-phenyl-1,1-diazanediylmethyl)-2-propenenitrile (**3a**).

A mixture of 2 (200 mg, 0.685 mmole) and triethyl orthoformate (250 mg, 1.69 mmoles) was refluxed in 30 ml of benzene for 4 hours. Crystals precipitated were filtered off, washed with benzene and dried to give 0.14 g (67% yield) of pure **3a**, mp 154-155° (recrystallized from ethanol-benzene); ms: m/z 302 ($M^+$); ir: 2195 $cm^{-1}$ (C≡N); pmr: δ 8.45 (8.38) [9] (s, 1H, imidazole ring), 7.70 [10] (s, 1H, N=CH), 8.45 (7.73) (b, 2H, $NH_2$), 10.03 (9.57) (s, 1H, NH), 6.60-7.80 [11] (m, aromatic).

*Anal.* Calcd. for $C_{17}H_{14}N_6 \cdot \frac{1}{2} H_2O$: C, 65.69; H, 4.70; N, 27.03. Found: C, 66.02; H, 4.66; N, 27.02.

3-Amino-3-(2-methylbenzimidazol-1-yl)-2-(2-phenyl-1,1-diazanediylmethyl)-2-propenenitrile (**3b**) and 3-Amino-3-(2-ethylbenzimidazol-1-yl)-2-(2-phenyl-1,1-diazanediylmethyl)-2-propenenitrile (**3c**).

The same method was used for synthesizing **3b** and **3c**.

Compound **3b** was obtained in 69% yield, mp 182-183° (recrystallized from ethanol-benzene); ms: m/z 316 ($M^+$); ir: 2195 $cm^{-1}$ (C≡N); pmr: δ 2.53 (2.48) (s, 3H, $CH_3$), 7.70 [10] (s, 1H, N=CH), 8.50 (7.80) (b, 2H, $NH_2$), 10.03 (9.57) (s, 1H, NH), 6.60-7.70 [11] (m, aromatic).

*Anal.* Calcd. for $C_{18}H_{16}N_6$: C, 68.34; H, 5.10; N, 26.56. Found: C, 68.37; H, 5.11; N, 26.26.

Compound **3c** was obtained in 79% yield, mp 162-163° (recrystallized from ethanol-benzene); ms: m/z 330 ($M^+$); ir: 2200 $cm^{-1}$ (C≡N; pmr: δ 1.37 (1.43) (t, J = 7.5 Hz, 3H, $CH_3$), 2.87 (2.82) (qr, J = 7.5 Hz, 2H, $CH_2$), 7.70 [10] (s, 1H, N=CH), 8.51 (7.82) (b, 2H, $NH_2$), 10.10 (9.60) (s, 1H, NH), 6.60-7.70 [11] (m, aromatic).

*Anal.* Calcd. for $C_{19}H_{18}N_6 \cdot 1/10\ H_2O$: C, 68.72; H, 5.49; N, 25.31. Found: C, 68.56; H, 5.48; N, 24.94.

General Procedure for Degradation of **3c** (Table I).

Compound **3c** (100 mg) was refluxed in 50 ml of xylene for 2.5 hours. The tlc (chloroform/methanol = 9/1) showed three spots which were identified as **5**, **3c**, and **4c**, respectively. After evaporation of the solvent, the residues were performed on a preparative tlc (silica gel) with chloroform-methanol (9:1) as eluant to isolate **5**, **3c**, and **4c**. Compound **3c** was recovered in 46% (45.8 mg).

When a mixture of **2** (200 mg, 0.685 mmole) and orthoester (for example, triethyl orthoformate: 250 mg, 1.69 mmoles) was refluxed in 30 ml of 1-butanol for 4 hours, **4a** and **5** were obtained in 100% total yield.

## REFERENCES AND NOTES

[1] This is a Part III in a series of "Ring Transformation of 4-Amino-1H-1,5-benzodiazepine-3-carbonitrile", Part II: See reference [3].

[2] A researcher who belongs to Zeria Pharmaceutical Co., Japan.

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[9] Chemical shifts of *Z*-form are shown in parentheses.

[10] The chemical shift of *Z*-form is in the aromatic region, and could not be identified.

[11] The region includes signals of both *E* and *Z* forms.

[12] For example, J. H. Wang, *Science*, **161**, 328 (1968); C. G. Swain and J. F. Brown Jr., *J. Am. Chem. Soc.* **74**, 2534 (1952).