Ring Transformation of 4-Amino-1*H*-1,5-benzodiazepine-3-carbonitrile and Ethyl 4-Amino-1*H*-1,5-benzodiazepine-3-carboxylate into Benzimidazole Derivatives with Amines

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The ring contraction of 4-amino-1*H*-1,5-benzodiazepine-3-carbonitrile hydrochloride **1** and ethyl 4-amino-1*H*-1,5-benzodiazepine-3-carboxylate hydrochloride **2** with aromatic primary amines into benzimidazole derivatives **3** and **4** was readily accomplished by heating in methanol. Benzodiazepine **1** also reacted with methylamine and ethylamine at about 40° to give ring-opened amine adducts **7** which were recyclized to **1** with hydrochloric acid.

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We have previously reported that the reaction of 4-amino-1*H*-1,5-benzodiazepine-3-carbonitrile hydrochloride **1** with nucleophiles such as hydroxide anions [1], hydroxylamine [2] and hydrazines [3] gave 2,4-diamino-3*H*-1,5-benzodiazepine, benzimidazole and pyrazole derivatives, respectively. The reactions initially lead to the ring-opened adducts which are formed by attack of the nucleophiles at 2-position of **1**, and subsequently, the adducts recyclize to those heterocycles. In continuation of these study, we found that **1** and ethyl 4-amino-1*H*-1,5-benzodiazepine-3-carboxylate hydrochloride **2** reacted with aromatic and aliphatic primary amines. This paper describes these results, especially the ring contraction of **1** and **2** into 2-(2-anilino-1-substituted-vinyl)benzimidazole derivatives.

When a suspension of **1** [4] in methanol was refluxed with an aromatic primary amine such as aniline, *p*-anisidine, *m*-toluidine and *m*-chloraniline, the red crystals of the starting benzodiazepine changed into a pale yellow powder of 2-(2-anilino-1-cyanovinyl)benzimidazoles **3a-d** [5] (Scheme 1, Table I). The structural elucidation of **3a-d** was based on elemental analysis and spectral data (Table II). In the ^{1}H-nmr spectra of these compounds, their olefinic protons showed signals at 8.33-8.53 ppm as a doublet due to the coupling with the phenylamino protons. This is characteristic in comparison with the finding that the olefinic proton of **1** showed a singlet signal at 7.23 ppm. Since the coupling constants (J_{CH-NH}) are 11-13 Hz, the olefinic protons of **3a-d** would be in the *trans* position to the phenylamino protons. This steric relation was also supported by the fact that the phenylamino protons were observed at lower field (about 12 ppm) as broad signals, because the phenomena could be interpreted by the formation of an intramolecular hydrogen bond between the amino proton and the nitrogen of the benzimidazole ring. These observation supported the proposed benzimidazole structures and excluded the structure **4** which could arise by simple substitution with the aromatic amines at 4-position of **1**.

Similar reactions of **2** [4] with the aromatic primary amines under the same conditions as described above led to 2-(2-anilino-1-ethoxycarbonylvinyl)benzimidazoles **5a-d** (Scheme 1, Table I) which showed analogous spectral properties to those of **3a-d** in the ^{1}H-nmr spectra (Table II). Compounds **5a**, **b** and **d** gave doublet signals due to not only the olefinic proton but also the phenylamino proton).

The conversion of **1** and **2** to **3** and **5**, respectively, can be interpreted by a mechanism *via* intermediates of the ring-opened adducts **6**, whose *o*-amino group attacks the amidino carbon to form the benzimidazole ring system.

Scheme 1

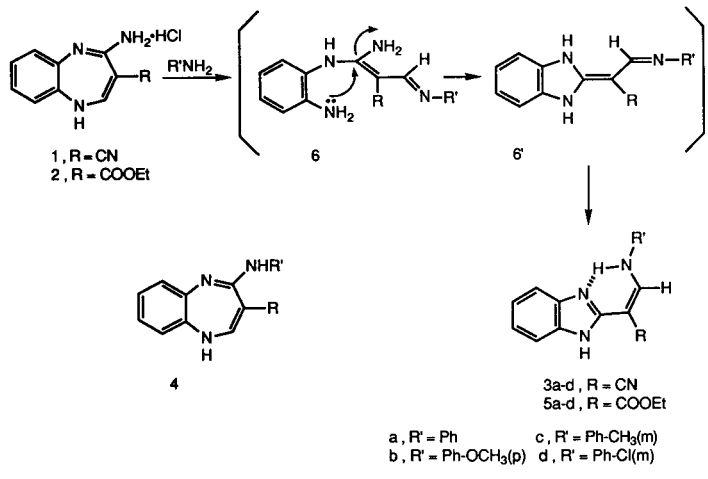


Table I

Physical Data for Compounds **3a-d** and **5a-d**

Compounds	Yield %	Mp°C	Molecular Formula	Analysis Calcd./Found % C	H	N
3a	55	246-248	$C_{16}H_{12}N_4$ (260.3)	73.83 73.44	4.65 4.67	21.53 21.53
3b	53	213-214	$C_{17}H_{14}N_4O$ (290.3)	70.33 70.33	4.86 4.84	19.30 19.25
3c	55	228-229	$C_{17}H_{14}N_4$ (274.3)	74.43 74.21	5.14 5.23	20.42 20.68
3d	48	245-246	$C_1H_{11}N_4Cl$ (294.8)	65.20 65.42	3.76 3.59	19.01 19.22
5a	48	163-164	$C_{18}H_{17}N_3O_2$ (307.4)	70.34 70.11	5.58 5.61	13.67 13.89
5b	62	165-166	$C_{19}H_{19}N_3O_3$ (337.4)	67.64 67.56	5.68 5.61	12.45 12.79
5c	65	150-151	$C_{19}H_{19}N_3O_2$ (321.38)	71.01 71.21	5.96 5.78	13.08 13.14
5d	24	170-171	$C_{18}H_{16}N_3O_2Cl$ (341.8)	63.25 63.38	4.72 4.86	12.29 12.17

Table II

Spectral Data for Compounds **3a-d** and **5a-d**

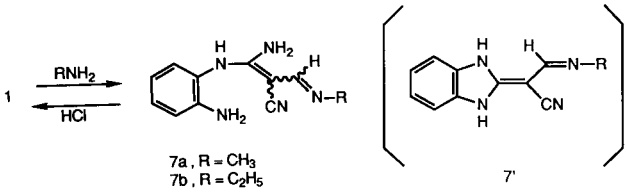
Compound No.	IR (cm^{-1}) KBr	MS m/z (M)	^{1}H-NMR (ppm) $CDCl_3$/DMSO-d_6 [a]
3a	3220, 2220, 1635	260	6.85-7.97 (9H, m, Ph-H), 8.50 (1H, d, J = 11 Hz, -CH=),12.16 (1H, s, NH), 12.45 (1H, br s, NH)
3b	3350, 2210	290	3.40 (3H, s, OCH_3), 6.92-7.86 (8H, m, Ph-H), 8.45 (1H, d, J = 11 Hz, -CH=), 12.31 (1H, br s, NH), 12.53 (1H, br s, NH)
3c	3260, 2210, 1640	274	2.38 (3H, s, CH_3), 6.91-7.65 (8H, m, Ph-H), 8.33 (1H, d, J = 13 Hz, -CH=), 12.2-12.5 (2H, br, 2NH)
3d	3280, 2220, 1640	294	6.77-7.66 (8H, m, Ph-H), 8.53 (1H, d, J = 12 Hz, -CH=), 12.1-12.5 (2H, br, 2NH)
5a	3400, 1670, 1640	307	1.40 (3H, t, J = 7 Hz, CH_2CH_3), 4.35 (2H, q, J = 7 Hz, CH_2CH_3), 7.10-7.63 (9H, m, Ph-H), 8.56 (1H, d, J = 13 Hz, -CH=), 11.89 (1H, br s, NH), 13.13 (1H, d, J = 13 Hz, NH)
5b	3400, 1650, 1520	337	1.38 (3H, t, J = 7 Hz, CH_2CH_3), 3.79 (3H, s, OCH_3), 4.33 (2H, q, J = 7 Hz, CH_2CH_3), 6.98-7.60 (8H, m, Ph-H), 8.47(1H, d, J = 13 Hz, -CH=), 11.90 (1H, br s, NH), 13.04 (1H, d, J = 13 Hz, NH)
5c	3390, 1660, 1640	321	1.42 (3H, t, J = 7 Hz, CH_2CH_3), 2.42 (3H, s, CH_3), 4.36 (2H, q, J = 7 Hz, CH_2CH_3), 6.94-7.73 (8H, m, Ph-H), 8.53 (1H, d, J = 11 Hz, -CH=), 11.19 (1H, br s, NH), 12.8-13.1 (1H, br, NH)
5d	3390, 16709, 1640	341	1.40 (3H, t, J = 7 Hz, CH_2CH_3), 4.35 (2H, q, J = 7 Hz, CH_2CH_3), 7.12-7.66 (8H, m, Ph-H), 8.53 (1H, d, J = 12 Hz, -CH=), 11.98 (1H, br s, NH), 13.24 (1H, d, J = 12 Hz, NH)

[a] Measured in DMSO-d_6 solution for **3a-b**.

Refluxing of **1** and an excess of aliphatic primary amine such as methylamine and ethylamine in methanol resulted in the formation of degradation products. However, when the reaction was carried out at about 40°, the ring-opened amine adducts **7a,b** were obtained as oily product (Scheme 2). The reaction of **2** with methylamine under the same conditions failed to give any significant product with decomposition of **2**. The structures of **7a,b** were determined on the basis of spectral data. Upon treatment with 2*N* hydrochloric acid, **7a,b** were recyclized to **1**, while they

decomposed in an alkaline solution. It should be noted that no formation of the benzimidazole of type **3** (R = CN, R′ = CH_3 or C_2H_5) was observed in these reactions. The above results suggest that **7a,b** could not be allowed to provide an intermediate **7′**, presumably, because of its instability. Whereas, the intermediate **6′** might be more stable because of the conjugated system with the terminal phenyl group, and that would readily tautomerize to the benzimidazole ring. This is why the aromatic amines reacted with **1** or **2** to give benzimidazole derivatives, whereas the aliphatic amines did not.

Scheme 2



EXPERIMENTAL

Melting points were determined using Köfler bench apparatus and are uncorrected. Nuclear magnetic resonance (^{1}H-nmr) spectra were measured with JEOL JNM-PMX 60 and GX-270 spectrometers with tetramethylsilane as internal standard. Mass spectra (ms) were taken on a JMS-DX 300 spectrometer (JEOL). Infrared (ir) spectra were recorded on a JASCO A-102 spectrophotometer.

2-(2-Anilino-1-cyanovinyl)benzimidazoles **3a-d**.

A mixture of **1** (0.55 g, 2.5 mmoles) and an aromatic amine (aniline, *p*-anisidine, *m*-toluidine or *m*-chloraniline, 10 mmoles) in methanol (10 ml) was refluxed for 2 hours (in the reaction with *p*-chloraniline, the heating was continued for 5 hours to complete the reaction) with stirring. After cooling, the precipitate was collected by filtration, washed with methanol and recrystallized from ethanol to yield **3a-d**. The data for these compounds are given in Tables I and II.

2-(2-Anilino-1-ethoxycarbonylvinyl)benzimidazoles **5a-d**.

A mixture of **2** (0.67 g, 2.5 mmoles) and an aromatic amine (aniline, *p*-anisidine, *m*-toluidine and *m*-chloraniline, 10 mmoles) in methanol (10 ml) was refluxed for 3 hours (in the reaction with *p*-chloraniline, the heating was continued for 9 hours to complete the reaction) with stirring. The precipitate was treated in the same manner as described above to yield **5a-d**. The data for these compounds are given in Tables I and II.

3-Amino-3-(*o*-aminoanilino)-2-cyano-1-alkylimino-2-propenes **a,b**.

A suspension of **1** (0.44 g, 2 mmoles) in 6% methanolic solution of methylamine or ethylamine (10 ml) was stirred at about 40° until the starting benzodiazepine **1** was completely dissolved (about 10 minutes). After removal of the solvent under reduced pressure below 30°, the residue was treated with water and the resulting mixture was extracted with ethyl acetate. The organic layer was washed with water, dried over magnesium sulfate and concentrated under reduced pressure to yield **7a** or **7b** as oily products which were practically pure by tlc examination.

Compound **7a** was obtained in 91% yield (0.39 g); ir: ν cm^{-1} 3470, 3360, 2190, 1650, 1570; ^{1}H-nmr (deuteriochloroform/-DMSO-d_6): δ 3.08 (3H, s, CH_3), 3.67 (2H, br s, NH_2), 4.76 (2H, br s, NH_2), 6.71-6.96 (4H, m, Ph-H), 7.25 (1H, s, -CH=), 9.8-11.0 (1H, br, NH); ms: m/z 215 (M^+), 108, 83 (100). High resolution ms: Calcd. for $C_{11}H_{13}N_5$: 215.1171. Found: 215.1141.

Compound **7b** was obtained in 92% yield (0.42 g); ir: ν cm^{-1} 3480, 3360, 2190, 1660, 1570; ^{1}H-nmr (deuteriochloroform/-DMSO-d_6): δ 1.32 (3H, t, J = 7 Hz, CH_2CH_3), 3.80 (2H, br s, NH_2), 3.90 (2H, q, J = 7 Hz, CH_2CH_3), 4.90 (2H, br s, NH_2), 6.77-7.01 (4H, m, Ph-H), 7.36 (1H, s, -CH=), 9.8-11.0 (1H, br, NH); ms: m/z 229 (M^+, 100), 108. High resolution ms: Calcd. for $C_{12}H_{15}N_5$: 229.1325. Found: 229.1307.

Formation of **1** from **7a,b**.

A solution of **7a** or **7b** (1 mmole) in 2*N* hydrochloric acid (5 ml) was kept at room temperature for 48 hours. The red crystalline precipitate was collected by filtration, washed with ethanol and dried to yield **1** (0.12 g, 54% from **7a**; 0.14 g, 63% from **7b**), mp 280-282° dec, which was identified by comparison of its ir and ^{1}H-nmr spectra with those of the authentic sample [4].

REFERENCES AND NOTES

[1] Y. Okamoto and K. Takagi, *J. Heterocyclic Chem.*, **24**, 885 (1987) and references cited therin.

[2] Y. Okamoto and K. Takagi, *J. Heterocyclic Chem.*, **26**, 277 (1989).

[3] Y. Okamoto, T. Ueda and K. Takagi, *Chem. Pharm. Bull.*, **31**, 2114 (1983).

[4] Y. Okamoto and T. Ueda, *J. Chem. Soc., Chem. Commun.*, 367 (1973).

[5] Compound **3a** has been synthesized by reaction between **1** and aniline without solvent in 35% yield; K. Takagi, T. Aotsuka, H. Morita and Y. Okamoto, *J. Heterocyclic Chem.*, **23**, 1443 (1986).