A Novel Synthesis of Pyrido[2,3-*b*][1,5]benzodiazepines

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A novel and convenient synthesis of the title compounds **4**, **5**, **11**, and **13** is described, involving the ring transformation of 1,5-benzodiazepine derivatives **1a** and **1b** with active methylene compounds.

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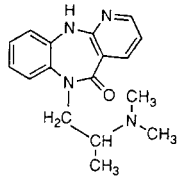
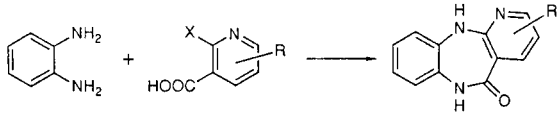
Many pyrido[2,3-*b*][1,5]benzodiazepines have been synthesized to evaluate their biological activities [1], and one of them, propizepine, appears to be active clinically [2]. So far the general method for synthesizing pyrido[2,3-*b*][1,5]-benzodiazepines is basically dependent on a condensation reaction of 2-aminoaniline with 2-halonicotinic acid [3] (Chart 1). However, the synthetic method has the disadvantage that a series of 2-halonicotinic acid derivatives as starting materials are not available readily. Recently, we have studied the ring transformations of 4-amino-1*H*-1,5-benzodiazepine-3-carbonitrile **1a** [4], which was readily synthesized by the reaction of 2-aminoaniline with ethoxymethylenemalononitrile [5], with some active methylene compounds under basic conditions, and 3-substituted-2-amino-6-(2-aminoanilino)-5-cyanopyridines **2a-d** [6] were obtained (Chart 2). In the present work, we synthesized 3-substituted-2-amino-6-(2-aminoanilino)-5-ethoxycarbonylpyridines **3a-d** from ethyl 4-amino-1*H*-1,5-benzodiazepine-3-carboxylate **1b**, and tried to produce pyrido[2,3-*b*][1,5]-benzodiazepine derivatives from **2a-d** and **3a-d** by intramolecular cyclizations.

Chart 1

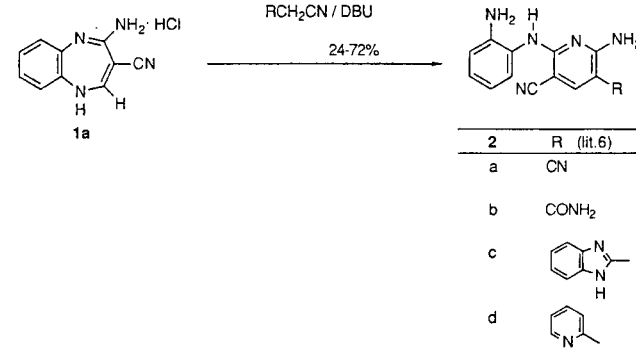


Propizepine



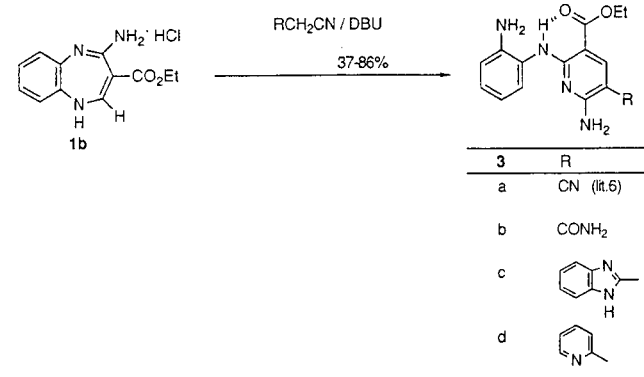
When **1b** was treated with active methylene compounds in the presence of 1,8-diazabicyclo[5,4,0]-7-undecene (DBU), the pyridine derivatives **3a-d** were obtained (Chart 3). Compounds **2a-d** and **3a-d** were intramolecularly cyclized to 3-substituted-2,5-diamino-11*H*-pyrido[2,3-*b*][1,5]-benzodiazepine **4a-d** and 3-substituted-2-aminopyrido[2,3-*b*][1,5]benzodiazepin-5(6*H*,11*H*)-ones **5a-d**, respectively, under reflux in acetic acid, while no cyclization occurred under reflux in alcohol or dimethylformamide in the presence of DBU (Chart 4), but the starting pyridine deriva-

Chart 2



2	R (lit.6)
a	CN
b	$CONH_2$
c	
d	

Chart 3



3	R
a	CN (lit.6)
b	$CONH_2$
c	
d	

Table

Compounds **3,4,5,11** and **13** [a]

Compound No.	Yield (%)	Mp (°C)	Molecular Formula	MS (M^+)	^{1}H-NMR δ (ppm)
3b	61	236-237	$C_{15}H_{17}N_5O_3$	315	1.34 (t, 3H, CH_3), 4.28 (q, 2H, CH_2), 4.73 (s, 2H, 2'-NH_2), 6.61-7.63 (m, 4H arom), 7.06 (b, 2H, 2-NH_2), 7.89 (b, 2H, $CONH_2$), 8.48 (s, 1H, 4-H), 9.82 (s, 1H, NH)
3c	50	258	$C_{21}H_{20}N_6O_2$	388	1.40 (t, 3H, CH_3), 4.36 (q, 2H, CH_2), 4.77 (s, 2H, 2'-NH_2), 6.66-7.71 (m, 4H arom + 2H, 2-NH_2), 7.18, 7.57 (m, 4H arom), 8.79 (s, 1H, 4-H), 9.87 (s, 1H, NH), 12.77 (s, 1H, NH)
3d	37	164	$C_{19}H_{19}N_5O_2$	349	1.36 (t, 3H, CH_3), 4.31 (q, 2H, CH_2), 4.73 (s, 2H, 2'-NH_2), 6.63-7.73 (m, 4H arom + 2H, 2-NH_2), 6.88 (dt, 1H, py-5-H), 7.25 (dt, 1H, py-4-H); 7.81 (dd, 1H, py-3-H), 8.49 (s, 1H, 4-H), 8.56 (dd, 1H, py-6-H)
4a	61	198-200	$C_{13}H_{10}N_6 \cdot CH_3COOH$	250	1.87 (s, 3H, CH_3), 6.78-6.93 (m, 4H arom), 7.15 (b, 2H, 2-NH_2 and b, 2H, 5-NH_2), 7.82 (s, 1H, 4-H), 8.21 (s, 1H, NH)
4b	78	207-208	$C_{13}H_{12}N_6O \cdot CH_3COOH$	268	1.84 (s, 3H, CH_3), 6.91-7.02 (m, 4H arom), 6.92, 7.26 (b, 2H, 2-NH_2), 7.76 (b, 2H, 5-NH_2), 8.06 (s, 1H, 4-H), 8.23 (b, 1H, NH), 8.80 (b, 2H, $CONH_2$)
4c	70	209-212	$C_{19}H_{15}N_7 \cdot CH_3COOH$	341	1.88 (s, 3H, CH_3), 6.99 (b, 2H, 2-NH_2), 6.64-7.67 (m, 8H arom), 7.55 (b, 1H, NH), 8.20 (b, 1H, NH), 8.32 (s, 1H, 4-H)
4d	40	223-224	$C_{17}H_{14}N_6 \cdot CH_3COOH$	302	1.87 (s, 3H, CH_3), 6.00-9.00 (b, 1H, NH + b, 2H, 2-NH_2 + b, 2H, 5-NH_2), 7.30, 7.47 (dd, 2H, 8-H, 9-H), 7.81, 9.10 (d, 2H, 7-H, 10-H), 7.21 (dd, 1H, py-5-H), 7.86 (dd, 1H, py-4-H), 8.48 (d, 1H, py-3-H), 8.62 (d, 1H, py-6-H)
5a	45	>300	$C_{13}H_9N_5O$	251	6.88-6.98, 7.07-7.13 (m, 4H arom), 7.18 (b, 2H, 2-NH_2), 8.11 (s, 1H, 4-H), 8.93 (s, 1H, 11-NH), 9.68 (s, 1H, 6-NH)
5b	75	>300	$C_{13}H_{11}N_5O_2$	269	6.83-7.00, 7.02-7.12 (m, 4H arom), 6.92, 7.08 (b, 2H, 2-NH_2), 7.40-8.20 (bd, 2H, $CONH_2$), 8.39 (s, 1H, 4-H), 8.57 (s, 1H, 11-NH), 9.56 (s, 1H, 6-NH)
5c	69	>300	$C_{19}H_{14}N_6O$	342	6.89-7.01, 7.09-7,24, 7.44-7.49, 7.60-7.65 (m, 8H arom), 8.56 (s, 1H, 11-NH), 8.69 (s, 1H, 4-H), 9.63 (s, 1H, 6-NH), 12.92 (s, 1H, imidazole-NH)
5d	89	240-245	$C_{17}H_{13}N_5O$	303	6.88-7.31 (m, 4H arom), 7.25 (dd, 1H, py-5-H), 7.78 (d, 1H, py-3-H), 7.83 (dd, 1H, py-4-H), 8.39 (s, 1H, 4-H), 8.43 (s, 1H, 11NH), 8.56 (d, 1H, py-6-H), 9.56 (s, 1H, 6-NH)
11	95	206-209	$C_{16}H_{16}N_4O_2$	296	1.29 (t, 3H, CH_3), 2.60 (s, 3H, CH_3), 4.25 (q, 2H, CH_2), 6.61 (b, 2H, NH_2), 6.72-6.92 (m, 4H arom), 8.09 (s, 1H, 4-H), 8.38 (s, 1H, NH)
13	13	237-240	$C_{16}H_{15}N_3O_3$	297	1.31 (t, 3H, CH_3), 2.62 (s, 3H, CH_3), 4.25 (q, 2H, CH_2), 6.92-7.18 (m, 4H arom), 8.52 (s, 1H, 4-H), 9.39 (s, 1H, 11-NH), 9.95 (s, 1H, 6-NH)

[a] The ir spectra (potassium bromide) showed the characteristic absorpion bands at 2200-2220 cm^{-1} (C≡N) for **3a-d** and **13**.

Chart 4

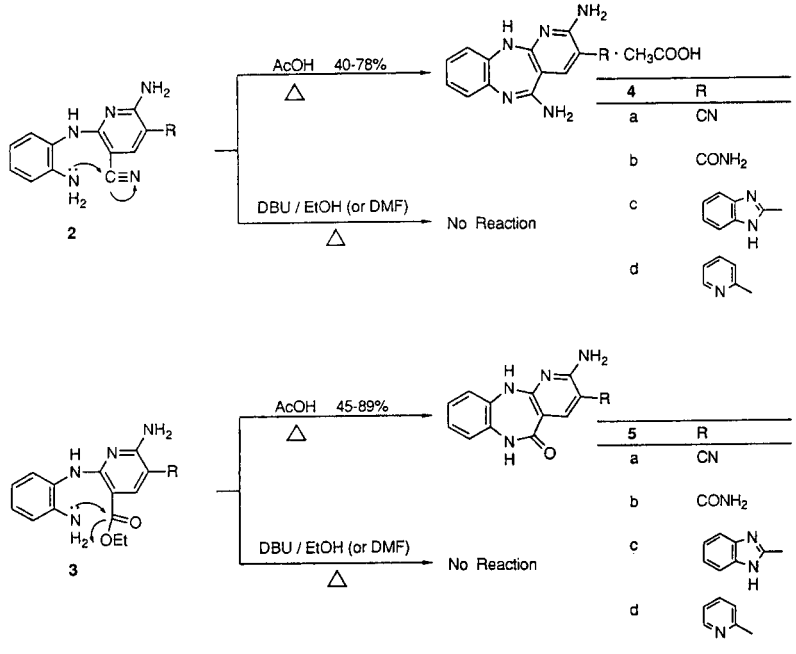


Chart 5

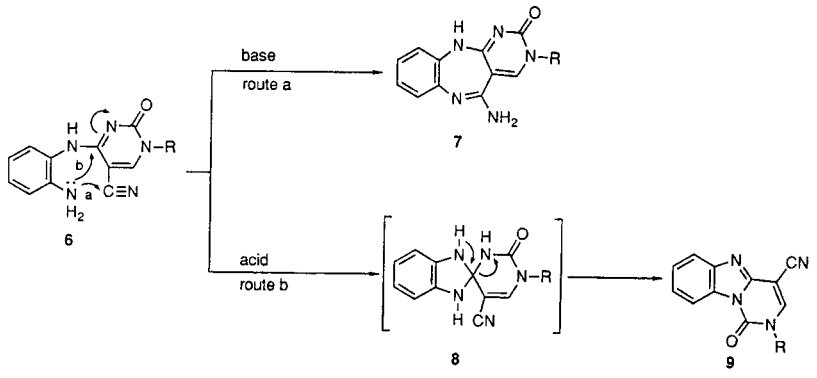
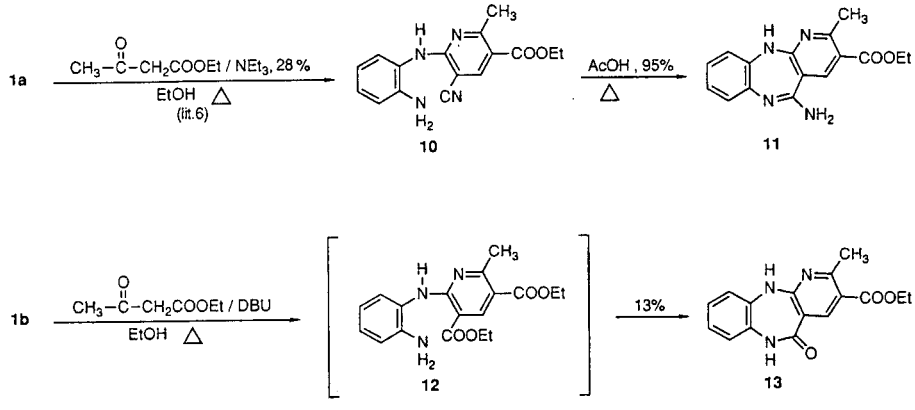


Chart 6



tives **2a-d** and **3a-d** were recovered. The structures of **4a-d** and **5a-d** were determined by spectroscopic analyses, especially for compounds **4b-d**, the disappearance of the infrared absorption band due to the cyano group of **2b-d**, and for compounds **5a-d** the observation of M^+ ion peak which is decreased by 46 mass units due to loss of ethanol from **3a-d**. Previously, we reported the intramolecular cyclization of 1-substituted-4-(2-aminoanilino)pyrimidin-2(1*H*)-one-5-carbonitrile **6** [7] where one cyclization proceeded under basic conditions to give 3-substituted-5-aminopyrimido[4,5-*b*][1,5]benzodiazepin-2(3*H*,11*H*)-ones **7** (route a in Chart 5), while under acidic conditions, the other cyclization proceeded to afford 2-substituted-pyrimido[1,6-*a*]benzimidazol-1(2*H*)-one-4-carbonitriles **9** (route b in Chart 5), probably *via* intermediates **8**. In the light of Baldwin's rule [8], it is worth noting that the intramolecular cyclization between amino and cyano groups in **2a-d** and **6** proceeds under different conditions, respectively.

A β-ketoester was also used as an active methylene compound. For example, the reaction of **1a** with ethyl acetoacetate under basic conditions gave 2-(2-aminoanilino)-3-cyano-5-ethoxycarbonyl-6-methylpyridine **10** [6] which was intramolecularly cyclized to 5-amino-3-ethoxycarbonyl-2-methyl-11*H*-pyrido[2,3-*b*][1,5]benzodiazepine **11** under acidic conditions. On the other hand, under basic conditions the reaction of **1b** with ethyl acetoacetate directly provided 3-ethoxycarbonyl-2-methylpyrido[2,3-*b*]-[1,5]benzodiazepin-5(6*H*,11*H*)-one **13** (Chart 6).

In conclusion, when compared with the method already known, our method for synthesizing pyrido[2,3-*b*][1,5]benzodiazepines is more useful from the following point of view: for one thing it is able to react with a variety of active methylene compounds including β-ketoesters which are more available than 2-halonicotinic acid derivatives, and for another thing it is able to derivatize the pyridine nucleus of the products **4**, **5**, **11** and **13** using their functional groups.

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 with a VXR-300 spectrometer at 300 MHz. The mass (ms) spectra were determined

with a JEOL 01S spectrometer. Elemental analyses were performed on a Perkin-Elmer 240B instrument.

3-Substituted-2-amino-6-(2-aminoanilino)-5-ethoxycarbonylpyridines **3b-d**.

General Procedure.

A mixture of **1b** (0.5 g, 1.87 mmoles) and 2-cyanoacetamide (0.17 g, 2.07 mmoles) in 50 ml of ethanol was refluxed for 5 hours in the presence of DBU (0.75 g, 4.9 mmoles). Precipitates of **3b** were collected by suction filtration, washed with ethanol and dried in a vacuum desiccator. The crude product is practically pure without further purification.

Anal. Calcd. for $C_{15}H_{17}N_5O_3$ **3b**: C, 57.44; H, 5.43; N, 22.21. Found: C, 57.10; H, 5.51; N, 21.99.

Anal. Calcd. for $C_{21}H_{20}N_6O_2 \cdot 4/5H_2O$ **3c**: C, 62.61; H, 5.40; N, 20.86. Found: C, 62.86; H, 5.24; N, 20.54.

Anal. Calcd. for $C_{19}H_{19}N_5O_2$ **3d**: C, 65.32; H, 5.48; N, 20.04. Found: C, 64.99; H, 5.44; N, 19.89.

3-Substituted-2,5-diamino-11*H*-pyrido[2,3-*b*][1,5]benzodiazepines **4a-d**.

General Procedure.

A suspension of **2a** (1 g, 4 mmoles) in 50 ml of acetic acid was refluxed for 4 hours. The solution was cooled (or allowed to stand) to precipitate bright yellow crystals of **4a** which were collected by suction filtration, washed with chloroform and dried in a vacuum desiccator. The crude product was practically pure without further purification.

Anal. Calcd. for $C_{13}H_{10}N_6 \cdot CH_3COOH \cdot 1/5H_2O$ **4a**: C, 57.39; H, 4.62; N, 26.77. Found: C, 57.06; H, 4.41; N, 26.76.

Anal. Calcd. for $C_{13}H_{12}N_6O \cdot CH_3COOH \cdot 6/5H_2O$ **4b**: C, 51.51; H, 5.30; N, 24.03. Found: C, 51.44; H, 5.09; N, 23.85.

Anal. Calcd. for $C_{19}H_{15}N_7 \cdot CH_3COOH$ **4c**: C, 62.83; H, 4.77; N, 24.42. Found: C, 63.17; H, 4.64; N, 24.73.

Anal. Calcd. for $C_{17}H_{14}N_6 \cdot CH_3COOH \cdot 1/5H_2O$ **4d**: C, 62.35; H, 5.07; N, 22.96. Found: C, 62.54; H, 4.91; N, 23.04.

3-Substituted-2-aminopyrido[2,3-*b*][1,5]benzodiazepin-5(6*H*,11*H*)-ones **5a-d**.

General Procedure.

A solution of **3a** (2.5 g, 8.42 mmoles) in 100 ml of acetic acid was refluxed for 3 hours. The solvent was evaporated under reduced pressure to provide crude **5a** which was recrystallized from chloroform and ethanol to give pure **5a**.

Anal. Calcd. for $C_{13}H_9N_5O \cdot 1/7H_2O$ **5a**: C, 61.52; H, 3.69; N, 27.59. Found: C, 61.54; H, 3.59; N, 27.55.

Anal. Calcd. for $C_{13}H_{11}N_5O_2 \cdot H_2O$ **5b**: C, 54.36; H, 4.53; N, 24.39. Found: C, 54.65; H, 4.25; N, 24.21.

Anal. Calcd. for $C_{19}H_{14}N_6O \cdot 1/2H_2O$ **5c**: C, 64.96; H, 4.27; N, 23.93. Found: C, 65.05; H, 3.98; N, 23.64.

Anal. Calcd. for $C_{17}H_{13}N_5O \cdot H_2O$ **5d**: C, 63.54; H, 4.71; N, 21.79. Found: C, 63.21; H, 4.57; N, 21.50.

5-Amino-3-ethoxycarbonyl-2-methyl-11*H*-pyrido[2,3-*b*][1,5]benzodiazepine **11**.

A solution of **10** (0.2 g, 6.76 mmoles) in 25 ml of acetic acid was refluxed for 3 hours. The solvent was removed under reduced pressure to afford yellow crystals of **11** which were washed with ethanol. The crude crystals were practically pure without further purification.

Anal. Calcd. for $C_{16}H_{16}N_4O_2$: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.70; H, 5.41; N, 18.63.

3-Ethoxycarbonyl-2-methylpyrido[2,3-*b*][1,5]benzodiazepin-5-(6*H*,11*H*)-one **13**.

A mixture of **1b** (0.5 g, 1.87 mmoles) and ethyl acetoacetate (0.28 g, 2.15 mmoles) in 50 ml of ethanol was refluxed for 3 hours in the presence of DBU (0.75 g, 4.9 mmoles). The solvent was removed under reduced pressure to afford a dark brown oil, which was allowed to stand for a week to provide yellow crystals of **13**. The crude crystals were washed with ethanol to give practically pure **13**.

Anal. Calcd. for $C_{16}H_{15}N_3O_3$: C, 64.64; H, 5.09; N, 14.13. Found: C, 64.38; H, 5.20; N, 14.12.

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