Convenient Syntheses of Pyrimidino[4,5-*b*][1,5]benzodiazepinones and Pyrimidino[1,6-*a*]benzimidazolones

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Pyrimidino[4,5-*b*][1,5]benzodiazepinones **4** and pyrimidino[1,6-*a*]benzimidazolones **5** were synthesized from 4-ethoxycarbonylamino-1*H*-1,5-benzodiazepine-3-carbonitrile (**2**) via ring transformation with some aliphatic primary amines. The reaction mechanisms for the formation of these compounds are proposed.

Much effort has recently been expended on the synthesis of fused tricyclic benzodiazepines because of their effective biological activities[1]. We previously studied the reactions of 4-amino-1*H*-1,5-benzodiazepine-3-carbonitrile **(1)** with nucleophiles such as hydroxide[2], hydroxylamine[3] and hydrazines[4]. However, our attempt to synthesize fused tricyclic systems such as pyrimidino[4,5-*b*][1,5]benzodiazepines from **1** was not successful[2]. In continuation of these studies, we found that 4-ethoxycarbonylamino-1*H*-1,5-benzodiazepine-3-carbonitrile **(2)**, prepared from **1** and ethyl chloroformate, also undergoes ring transformation with aliphatic primary amines to readily give cytosine derivatives **3a-d**, which are key intermediates in the formation of pyrimidino[4,5-*b*][1,5]benzodiazepinone and pyrimidino[1,6-*a*]benzimidazolone derivatives, **4a-d** and **5a-d**, respectively. This paper describes new and convenient syntheses of these compounds.

Treatment of **1** with ethyl chloroformate in ethanol in the presence of triethylamine at room temperature for 1 h provided a deep red crystalline precipitate of **2**, whose structure was elucidated on the basis of spectral data. In particular, ^{1}H-NMR spectrum of **2** showed signals at $\delta = 6.97$ ppm (br) and 10.71 ppm (s) due to one amino proton and one amido proton, respectively. This observation indicates that the ethoxycarbonyl group was attached not to the nitrogen atom in the diazepine nucleus, but to the amino group at the 4-position. When a suspension of **2** in ethanol was stirred with an aliphatic primary amine such as methylamine, ethylamine, *iso*-propylamine and *n*-butylamine at room temperature for 24 h, 1-substituted-4-(2-aminoanilino)pyrimidin-2(1*H*)-one-5-carbonitriles **3** were

obtained (Table). The spectral data of these compounds supported the proposed structures. Especially, the difference of chemical shifts of the olefinic protons between **2** (δ = 7.23 ppm) and **3a-d** (δ = 8.60–8.67 ppm) in ^{1}H-NMR spectra, and the observation of the fragment M^+-NCO ion peak in mass spectra of **3** excluded the structure **3'**, which could arise by simple condensation of the amines with the ethoxycarbonyl group of **2**. When **2** was treated with *tert*-butylamine or aniline under the same conditions as described above, no reaction was found to occur.

The compounds **3** undergo intramolecular cyclization to give two different tricyclic ring systems **4** and **5** depending on the reaction conditions used. Thus, refluxing of **3** with an excess of triethylamine in ethanol for 72 h gave 3-substituted-5-aminopyrimidino[4,5-*b*][1,5]benzodiazepin-2(3*H*, 11*H*)-ones **4** (Table) as yellow crystalline precipitate. On the other hand, the heating of **3** in ethanol in the presence of 3 mol equivalent amounts of *p*-toluenesulfonic acid for 2 h afforded 2-substituted-pyrimidino[1,6-*a*]benzimidazol-1(2*H*)-one-4-carbonitriles **5** in good yield (Table). The structural assignment of **4** and **5** is based on microanalyses, mass- and ^{1}H-NMR spectral data.

There is no change of the molecular weight between **3** and **4**. In the IR spectra, **4** showed no absorption band at nitrile region. On the other hand, **5** were formed by elimination of ammonia from **3**. The IR spectra of **5** showed absorption bands due to C≡N and C=O. In the ^{1}H-NMR spectra of **5**, one of the aromatic proton signals 9-H was observed at lower field. This is characteristic for pyrimidino[1,6-*a*]benzimidazol-1-one structural type[5] due to the paramagnetic anisotropy of the carbonyl group at 1-position.

Table. Compounds **3**, **4** and **5** prepared

Product No.	Yield [%]	m.p.[a] [°C]	Molecular Formula[b]	M.S.[c], *m/e* (M^+)	(M^+—NCO)	^{1}H-NMR[d] δ [ppm]
3a	72	215–217 (decomp.)	$C_{12}H_{11}N_5O$ (241.3)	241	199	3.30 (s, 3H, CH_3); 4.3–6.0 (br, 2H, NH_2); 6.31–7.27 (m, 4H$_{arom}$); 7.5–9.3 (br, 1H, NH); 8.62 (s, 1H, =CH)
3b	50	192–193	$C_{13}H_{13}N_5O$ (255.3)	255	213	1.20 (t, 3H, J = 8 Hz, CH_2—CH_3); 3.79 (q, 2H, J = 8 Hz, CH_2—CH_3); 4.4–6.0 (br, 2H, NH_2); 6.43–7.40 (m, 4H$_{arom}$); 7.8–9.9 (br, 1H, NH); 8.67 (s, 1H, =CH)
3c	56	188–191	$C_{14}H_{15}N_5O$ (269.3)	269	227	1.25 [d, 6H, J = 7 Hz, $CH(CH_3)_2$]; 4.2–5.8 (br, 2H, NH_2); 4.7 (hep, 1H, J = 7 Hz, CH); 6.37–7.27 (m, 4H$_{arom}$); 7.5–9.2 (br, 1H, NH); 8.60 (s, 1H, =CH)
3d	53	179–181	$C_{15}H_{17}N_5O$ (283.3)	283	241	0.77–1.97 [m, 7H, —$(CH_2)_2CH_3$]; 3.73 (t, 2H, J = 7 Hz, N—CH_2—); 4.5–5.9 (br, 2H, NH_2); 6.37–7.33 (m, 4H$_{arom}$); 8.0–9.6 (br, 1H, NH); 8.62 (s, 1H, =CH)
4a	55	282–285 (decomp.)	$C_{12}H_{11}N_5O$ (241.3)	241	199	3.33 (s, 3H, CH_3); 4.0–9.4 (br, 3H, NH, NH_2); 6.57–7.27 (m, 4H$_{arom}$); 8.15 (s, 1H, =CH)
4b	66	277–280 (decomp.)	$C_{13}H_{13}N_5O$ (255.3)	255	213	1.27 (t, 3H, J = 8 Hz, CH_2—CH_3); 3.80 (q, 2H, J = 8 Hz, CH_2—CH_3); 6.3–8.7 (br, 3H, NH, NH_2); 6.63–7.20 (m, 4H$_{arom}$); 8.17 (s, 1H, =CH)
4c	32	247–250 (decomp.)	$C_{14}H_{15}N_5O$ (269.3)	269	227	1.32 [d, 6H, J = 7 Hz, $CH(CH_3)_2$]; 4.63 (hep, 1H, J = 7 Hz, CH); 5.6–8.3 (br, 3H, NH, NH_2); 6.57–7.10 (m, 4H$_{arom}$); 7.97 (s, 1H, =CH)
4d	59	254–258 (decomp.)	$C_{15}H_{17}N_5O$ (283.3)	283	241	0.73–2.03 [m, 7H, —$(CH_2)_2CH_3$]; 3.78 (t, 2H, J = 7 Hz, N—CH_2—); 6.6–8.7 (br, 3H, NH, NH_2); 6.67–7.13 (m, 4H$_{arom}$); 8.15 (s, 1H, =CH)
5a	69	>300	$C_{12}H_8N_4O$ (224.2)	224		3.97 (s, 3H, CH_3); 7.63–8.10 (m, 3H$_{arom}$); 8.53–8.90 (m, 1H$_{arom}$); 8.78 (s, 1H, =CH)
5b	80	270–271	$C_{13}H_{10}N_4O$ (238.3)	238		1.65 (t, 3H, J = 7 Hz, CH_2—CH_3); 4.48 (q, 2H, J = 7 Hz, CH_2—CH_3); 7.67–8.10 (m, 3H$_{arom}$); 8.63–9.03 (m, 1H$_{arom}$); 8.83 (s, 1H, =CH)
5c	90	282–283	$C_{14}H_{12}N_4O$ (252.3)	252		1.70 [d, 6H, J = 7 Hz, $CH(CH_3)_2$]; 5.33 (hep, 1H, J = 7 Hz, CH); 7.77–8.00 (m, 3H$_{arom}$); 8.60–8.87 (m, 1H$_{arom}$); 8.80 (s, 1H, =CH)
5d	71	179–181	$C_{15}H_{14}N_4O$ (266.3)	266		0.80–2.32 [m, 7H, —$(CH_2)_2CH_3$]; 4.40 (t, 2H, J = 7 Hz, N—CH_2—); 7.60–8.15 (m, 3H$_{arom}$); 8.53–8.97 (m, 1H$_{arom}$); 8.82 (s, 1H, =CH)

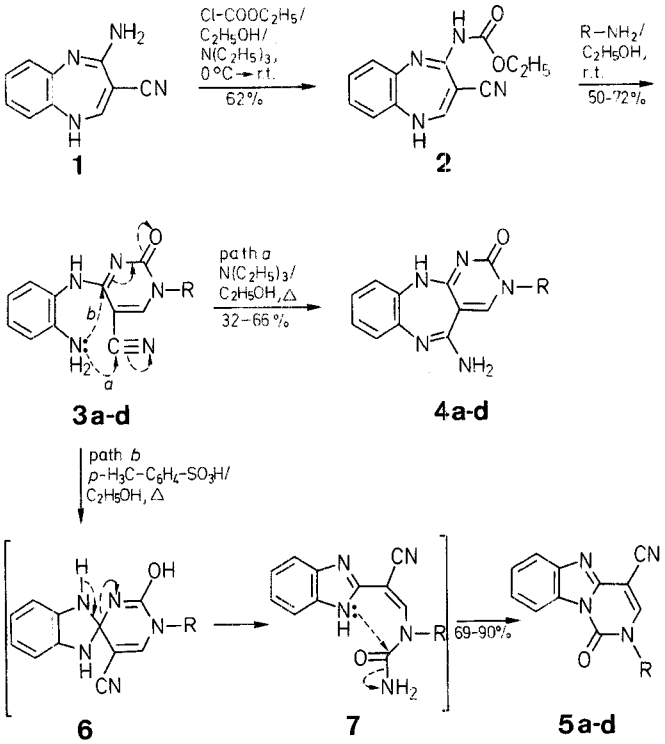
[a] Melting points are uncorrected.

[b] Products **3a–d**, **4d** and **5a–d** gave satisfactory microanalyses: C ±0.33, H ±0.06, N ±0.15. Products **4a–c** gave satisfactory high resolution mass spectra: **4a**: calc. 241.0964, found 241.0959; **4b**: calc. 255.1120, found 255.1136; **4c**: calc. 269.1276, found 269.1287.

[c] Obtained on a JEOL JMS D-300 spectrometer.

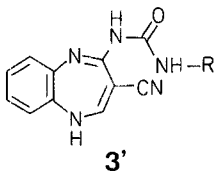
[d] Obtained on a JEOL-C60H spectrometer in DMSO-d_6 solution for **3a–d** and **4a–d**, and CF_3COOD solution for **5a–d**. The IR spectra (KBr) showed the characteristic absorptions at 3460–3310 cm^{-1} (N—H), 2240–2220 cm^{-1} (C≡N) and 1665–1660 cm^{-1} (C=O) for **3a–d**; 3475–3270 cm^{-1} (N—H) and 1650–1635 cm^{-1} (C=O) for **4a–d**; and 2250–2220 cm^{-1} (C≡N) and 1715–1710 cm^{-1} (C=O) for **5a–d**.

We suggest possible mechanisms for the formation of **4** and **5** in the Scheme. In the base-catalyzed cyclization, the interaction between the cyano group and the *o*-amino group in **3** is predominant (reaction *a*). Whereas in the acid-catalyzed cyclization, the *o*-amino group attacks at 4-position of pyrimidine nucleus in **3** (reaction *b*) to give spiro-intermediate **6** which is readily converted to **7**, and recyclization of **7** gives **5** with loss of ammonia. Similar cleavage of pyrimidine ring has been described for ethyl 4-(2-aminoanilino) pyrimidine-5-carboxylate in acid[6].



1 **2** **3a-d** **4a-d** **6** **7** **5a-d**

3–7	R
a	CH_3
b	C_2H_5
c	i-C_3H_7
d	n-C_4H_9[7]



3'

4-Ethoxycarbonylamino-1*H*-1,5-benzodiazepine-3-carbonitrile (2):
Ethyl chloroformate (7.8 g, 72 mmol) is added dropwise to a suspension of benzodiazepine **1** (11.1 g, 60 mmol) in ethanol (60 ml) containing triethylamine (7.3 g, 72 mmol), with stirring at about 0 °C. Stirring is continued for 1 h at room temperature. The precipitate is collected, washed with ethanol (30 ml) and recrystallized from dimethylformamide/ethanol to yield **2** as deep red crystals; yield: 9.5 g (62%); m.p. 240 °C (decomp.).

$C_{13}H_{12}N_4O_2$ (256.3) calc. C 60.93 H 4.72 N 21.87
found 60.79 4.70 21.57

IR (KBr): ν = 3270, 3220, 2200, 1660 cm^{-1}.

^{1}H-NMR (DMSO-d_6/TMS): δ = 1.27 (t, 3H, J = 8 Hz, CH_2—CH_3); 4.18 (q, 2H, J = 8 Hz, CH_2—CH_3); 6.50–7.33 (m, 4H arom); 6.97 (br, 1H, NH); 7.23 (s, 1H olefinic); 10.71 (br, 1H, CONH).

MS (FAB): m/e = 257 (M^+ + H).

1-Substituted-4-(2-aminoanilino)pyrimidin-2(1*H*)-one-5-carbonitriles (3a-d); General Procedure:
A mixture of **2** (2.56 g, 10 mmol) and an aliphatic primary amine (15 mmol) in ethanol (40 ml) is stirred at room temperature for 24 h. The yellow precipitate is collected, washed with ethanol and recrystallized from dimethylformamide/ethanol (for **3a**) or ethanol/ethyl acetate (for **3b-d**).

3-Substituted-5-aminopyrimidino[4,5-*b*][1,5]benzodiazepin-2(3*H*, 11*H*)-ones (4a-d); General Procedure:
A mixture of **3a-d** (10 mmol) and triethylamine (5 ml) in ethanol (100 ml) is refluxed for 72 h. After cooling, the crystalline solid is collected, washed with ethanol and dried to yield **4a-d**. The crude products are practically pure without further purification, which is difficult because of the insolubility in ordinary organic solvents.

2-Substituted-pyrimidino[1,6-*a*]benzimidazol-1(2*H*)-one-4-carbonitriles (5a-d); General Procedure:
A mixture of **3a-d** (4 mmol) and *p*-toluenesulfonic acid (2.06 g, 12 mmol) in ethanol (30 ml) is refluxed for 2 h. After cooling, the precipitate is collected, washed with ethanol and recrystallized from dimethylformamide/ethanol to yield **5a-d**.

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