Synthesis of Pyrimidino[4,5-*b*][1,5]benzodiazepin-2-ones and Pyrimidino[1,6-*a*]benzimidazol-1-ones from 4-Ethoxycarbonylamino-1*H*-1,5-benzodiazpine-3-carbonitrile *via* 4-(2-Aminoanilino)pyrimidin-2(1*H*)-one-5-carbonitriles

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Reactions of 4-ethoxycarbonylamino-1*H*-1,5-benzodiazepine-3-carbonitrile (**2**) with aliphatic primary amines gave 1-substituted 4-(2-aminoanilino)pyrimidin-2(1*H*)-one-5-carbonitriles **3**. Analogous reactions of **2** with aromatic primary amines afforded 2-(2'-anilino-1'-cyanovinyl)benzimidazoles **5** and **6**. Upon treatment with triethylamine, **3** underwent intramolecular cyclization to give 3-substituted 5-aminopyrimidino[4,5-*b*][1,5]benzodiazepin-2(3*H*,11*H*)-ones **8**. Heating of **3** with *p*-toluenesulfonic acid in ethanol gave 2-substituted pyrimidino[1,6-*a*]benzimidazol-1(2*H*)-one-4-carbonitriles **9**. Reactions of **2** with hydrazines were also described. Mechanistic pathways are proposed to account for the products.

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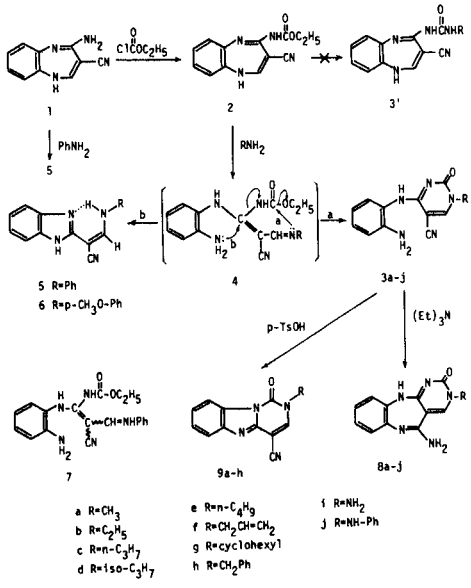
Extensive studies have been carried out for synthesizing fused tricyclic benzodiazepines because of their effective biological activities [1]. In the previous papers [2], we reported the ring transformation of 4-amino-1*H*-1,5-benzodiazepine-3-carbonitrile (**1**), which involves ring opening in the diazepine nucleus by nucleophilic attack of hydroxylamine and hydrazine. However, our attempt to synthesize fused tricyclic systems such as pyrimidino[4,5-*b*][1,5]-benzodiazepines of biological interest [3] by annulation of amidino moiety on the diazepine ring of **1** was not successful [4]. In continuation of the above studies, we found that 4-ethoxycarbonylamino-1*H*-1,5-benzodiazepine-3-carbonitrile (**2**) undergoes ring transformation with various aliphatic primary amines to give pyrimidine derivatives **3** which are effective key intermediates in the formation of two different tricyclic ring system: pyrimidino[4,5-*b*][1,5]benzodiazepin-2-one and pyrimidino[1,6-*a*]benzimidazol-1-one. This paper describes these results including full details of the previous work [5].

Compound **2** was readily prepared by treatment of **1** with ethyl chloroformate in ethanol in the presence of triethylamine at room temperature. The structure of **2** was determined on the basis of analytical and spectral data. In particular, the ^{1}H-nmr spectrum of **2** showed signals at δ 6.97 ppm (br, 1H) and δ 10.17 ppm (br, 1H) assignable to one amino proton and one amido proton, respectively. This observation suggests that the ethoxycarbonyl group was attached not to the nitrogen atom in the diazepine nucleus, but to the amino group at 4-position. When a suspension of **2** in ethanol was stirred with methylamine at room temperature for 24 hours, the deep red crystals of **2** changed into a pale yellow powder of 1-methyl-4-(2-aminoanilino)pyrimidin-2(1*H*)-one-5-carbonitrile (**3a**). Similar reactions of **2** with various aliphatic primary amines gave the corresponding pyrimidines **3b-h**, respectively (Scheme 1, Table I and II). The structural elucidation of these compounds was based on elemental analysis and spectral data. Especially, in the ^{1}H-nmr spectra of **3a-h**, the signal due to the olefinic protons (δ 8.55-8.83 ppm) was observed at lower field than that of the olefinic proton (δ 7.23 ppm) in the spectrum of **2**. This difference of chemical shift and the observation of M^+-NCO and/or M^+-HNCO fragments ion peaks in the mass spectra of **3a-h** excluded the structures **3'** which could arise by simple condensation of the amines with the ethoxycarbonyl group of **2**. The pathway to the pyrimidines **3** can be rationalized by initial attack of the amines at 2-position of **2** to give ring-opened intermediates **4**, followed by liberation of ethanol from **4** to afford **3** (reaction a in Scheme 1). Under the same conditions as described above, **2** could not react with *t*-butylamine, and was recovered. When the reaction was carried out under reflux in ethanol, the decomposition of **2** was observed. The reason for these facts might be steric hindrance of the bulky amine.

Reactions of **2** with aromatic primary amines such as aniline and *p*-anisidine at room temperature did not proceed. Refluxing of **2** with aniline in ethanol for 3 hours resulted in the formation of 2-(2'-anilino-1'-cyanovinyl)benzimidazole (**5**) which was also obtained by reacting **1** with aniline (Scheme 1). Compound **5** should be produced from a presumed intermediate of type **4** (R = C_6H_5) by predominant attack of the *o*-amino group to the amidino carbon in **4** (reaction b in Scheme 1) with liberation of urethane. Low nucleophilicity of the aromatic amine may be

responsible for the formation of **5** from **2**. In the ^{1}H-nmr spectrum of **5**, coupling between a phenylamino proton and an olefinic proton was observed. The constant is $J_{NH\text{-}CH}$ = 11 Hz, which indicates they are in a *trans* relation. The signal for the phenylamino proton was observed at lower magnetic field (δ 12.45 ppm). This may indicate the formation of a hydrogen bond between the amino proton and the nitrogen of the benzimidazole ring. Similar reaction of **2** with *p*-anisidine in boiling ethanol afforded 2-[1'-cyano-2'-(4-methoxyanilino)vinyl]benzimidazole (**6**) which showed analogous spectral properties to that of **5**.

Scheme 1



We also found that hydrazines readily react with **2** in a similar mode to that of aliphatic primary amines to give pyrimidines. Treatment of **2** with hydrazine hydrate in ethanol at room temperature for 3 hours gave 1-amino-4-(2-aminoanilino)pyrimidin-2(1*H*)-one-5-carbonitrile (**3i**) (Scheme 1, Table I and II). However, a similar reaction of **2** with phenylhydrazine gave a ring opened phenylhydrazine adduct: 3-ethoxycarbonylamino-3-(2-aminoanilino)-2-cyano-2-propenyl phenylhydrazone (**7**) which was converted into 1-anilino-4-(2-aminoanilino)pyrimidin-2(1*H*)-one-5-carbonitrile (**3j**) by heating with triethylamine in ethanol for 2 hours. The ^{1}H-nmr study of **7** revealed that it consisted of two stereoisomers.

Treatment of **3a-j** with an excess of triethylamine in boiling ethanol for 72 hours gave 3-substituted 5-aminopyrimidino[4,5-*b*][1,5]benzodiazepin-2(3*H*,11*H*)-ones **8a-j** (Scheme 1, Table III and IV). The purification of these compounds was generally difficult because of their insolubility in ordinary organic solvents. However, the crude products were practically pure without further purification. The structures of **8a-j** were supported by the spectral data, especially the mass (no change of molecular weight between **3a-j** and **8a-j**), ir (no absorption band in nitrile region) and ^{1}H-nmr spectra. To the best of our knowledge, only two reports have appeared on the synthesis of another examples of 3-substituted pyrimidino[4,5-*b*][1,5]benzodiazepin-2-ones [6].

On the other hand, heating of **3a** in ethanol in the presence of 3 moles equivalent amounts of *p*-toluenesulfonic acid for 2 hours gave 2-methylpyrimidino[1,6-*a*]benzimidazol-1(2*H*)-one-4-carbonitrile (**9a**) in 69% yield (Scheme 1,

Table I

Physical Data for Compounds **3a-i**

Compound No.	R	Yield %	Mp °C Recrystallization solvent	Molecular Formula	Analyses Calcd. % Found % C	H	N
3a	CH_3	72	215-217	$C_{12}H_{11}N_5O$	59.74	4.60	29.03
			DMF-EtOH	(241.26)	59.45	4.60	28.83
3b	C_2H_5	50	192-193	$C_{13}H_{13}N_5O$	61.17	5.13	27.43
			DMF-EtOH	(255.28)	60.94	5.12	27.32
3c	*n*-C_3H_7	43	182-184	$C_{14}H_{15}N_5O$	62.44	5.61	26.01
			C_6H_6-EtOH	(269.31)	62.05	5.59	25.93
3d	*iso*-C_3H_7	56	188-191	$C_{14}H_{15}N_5O$	62.44	5.61	26.01
			C_6H_6-EtOH	(269.31)	62.52	5.62	25.92
3e	*n*-C_4H_9	53	179-181	$C_{15}H_{17}N_5O$	63.59	6.05	24.72
			C_6H_6-EtOH	(283.34)	63.26	6.03	24.69
3f	$CH_2CH=CH_2$	60	164-166	$C_{14}H_{13}N_5O$	62.91	4.90	26.20
			EtOH	(267.29)	62.70	4.89	26.07
3g	C_6H_{11}	53	215-217	$C_{17}H_{19}N_5O$	66.00	6.19	22.64
			EtOH	(309.37)	65.62	6.19	22.56
3h	CH_2Ph	49	205-206	$C_{18}H_{15}N_5O$	68.12	4.76	22.07
			EtOH	(317.35)	68.11	4.73	22.01
3i	NH_2	78	198-201	$C_{11}H_{10}N_6O$	54.54	4.16	34.70
			DMF-EtOH	(242.24)	54.51	4.05	34.91

Table II

Spectral Data for Compounds **3a-i**

Compound No.	IR (cm^{-1}) KBr	MS [a] m/z	^{1}H-NMR (ppm) DMSO-d_6
3a	3460, 3350, 3280, 2220, 1655	241 (M^+) 199 (M^+-NCO)	3.30 (s, 3H), 4.3-6.0 (br, 2H), 6.31-7.27 (m, 4H), 7.5-9.3 (br, 1H), 8.62 (s, 1H),
3b	3460, 3360, 3230, 2230, 1655	255 (M^+) 213 (M^+-NCO)	1.20 (t, J = 8 Hz, 3H), 3.79 (q, J = 8 Hz, 2H), 4.80 (br s, 2H), 6.43-7.40 (m, 4H), 7.8-9.9 (br, 1H), 8.67 (s, 1H)
3c	3450, 3350, 2220, 1665	269 (M^+) 227 (M^+-NCO)	0.85 (t, J = 7 Hz, 3H), 1.33-1.90 (m, 2H), 3.73 (t, J = 8 Hz, 2H), 4.0-6.2 (br, 2H), 6.40-7.23 (m, 4H), 7.8-9.2 (br, 1H), 8.73 (s, 1H)
3d	3430, 3380, 3340, 2230, 1660	269 (M^+) 227 (M^+-NCO)	1.25 (d, J = 7 Hz, 6H), 4.90 (br s, 2H), 4.70 (hep, J = 7 Hz, 1H), 6.37-7.27 (m, 4H), 7.5-9.2 (br, 1H), 8.60 (s, 1H)
3e	3450, 3380, 3350, 2230, 1665	283 (M^+) 241 (M^+-NCO) 240 (M^+-HNCO)	0.77-1.97 (m, 7H), 3.73 (t, J = 7 Hz, 2H), 5.00 (br s, 2H), 6.37-7.33 (m, 4H), 8.0-9.6 (br, 1H), 8.62 (s, 1H)
3f	3490, 3400, 3310, 2240, 1660	267 (M^+) 225 (M^+-NCO)	4.2-6.0 (br, 2H), 4.35 (d, J = 5 Hz, 2H), 4.97-6.33 (m, 3H), 6.43-7.27 (m, 4H), 7.9-9.4 (br, 1H), 8.62 (s, 1H)
3g	3420, 3350, 3330, 2220, 1660	309 (M^+) 267 (M^+-NCO)	0.93-2.17 (m, 10H), 4.0-5.2 (br, 3H), 6.40-7.30 (m, 4H), 8.0-9.5 (br, 1H), 8.70 (s, 1H)
3h	3450, 3380, 3340, 2230, 1670	317 (M^+) 274 (M^+-HNCO)	4.0-6.0 (br, 2H), 4.95 (s, 2H), 6.40-7.30 (m, 4H), 7.37 (s, 5H), 8.4-9.3 (br, 1H), 8.83 (s, 1H)
3i	3480, 3380, 3280, 2240, 1650	243 $(M+H)^+$ 335 (M + H + glycerol)$^+$	4.4-5.9 (br, 2H), 5.73 (s, 2H), 6.40-7.20 (m, 4H), 7.8-9.4 (br, 1H), 8.55 (s, 1H)

[a] Measured by FAB(+) method for **3i**.

Table III

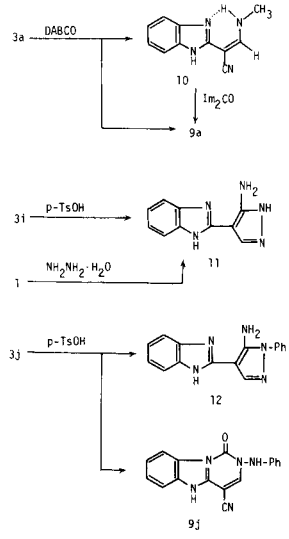
Physical Data for Compounds **8a-j**

Compound No.	R	Yield %	Mp °C	Molecular Formula	High Resolutions MS m/z or Analyses Calcd. % Found% C	H	N
8a	CH_3	55	282-285	$C_{12}H_{11}N_5O$ (241.26)	241.0964 (M^+) 241.0959		
8b	C_2H_5	66	277-280	$C_{13}H_{13}N_5O$ (255.28)	255.1120 (M^+) 255.1136		
8c	*n*-C_3H_7	55	249-251	$C_{14}H_{15}N_5O$ (269.31)	269.1276 (M^+) 269.1237		
8d	*iso*-C_3H_7	32	247-250	$C_{14}H_{15}N_5O$ (269.31)	269.1276 (M^+) 269.1287		
8e	*n*-C_4H_9	59	254-258	$C_{15}H_{17}N_5O$ (283.34)	63.58 63.69	6.05 6.18	24.72 24.93
8f	$CH_2CH=CH_2$	59	245-250	$C_{14}H_{13}N_5O$ (267.29)	267.1119 (M^+) 267.1121		
8g	C_6H_{11}	75	274-276	$C_{17}H_{19}N_5O$ (309.37)	66.00 65.65	6.19 6.23	22.64 22.27
8h	CH_2-Ph	73	267-269	$C_{18}H_{15}N_5O$ (317.35)	317.1277 (M^+) 317.1284		
8i	NH_2	50	291-295	$C_{11}H_{10}N_6O$ (242.24)	54.54 54.30	4.16 4.13	34.70 34.47
8j	NH-Ph	46	197-200	$C_{17}H_{14}N_6O$ (318.34)	318.1197 (M^+) 318.1165		

Table V and VI). The characterization of **9a** was based on the following evidence. The mass and elementary analyses established the molecular formula as $C_{12}H_8N_4O$, which corresponded to the loss of ammonia from **3a**. The ir spectrum of **9a** revealed the cyano and carbonyl absorption bands at 2240 and 1715 cm^{-1}, respectively. In the ^{1}H-nmr spectrum of **9a**, the signal for one of the aromatic protons was observed at lower field (δ 8.53-8.90 ppm), and it was attributed to C_9-H proton because of the paramagnetic anisotropy of the carbonyl group at 1-position [7]. Additional support for the structure **9a** was obtained by its unequivocal synthesis from 2-(1'-cyano-2'-methylaminovinyl)-benzimidazole (**10**) [8]. Namely, refluxing of **3a** in ethanol with an excess of 1,4-diazabicyclo[2.2.2]octane (DABCO)

afforded **9a** and **10** in 22 and 23% yields, respectively. The structure of **10**, which are comparable with that of **5**, was assigned by analytical and spectral data. Reaction of **10** with *N,N'*-carbonyldiimidazole (Im_2CO) in refluxing tetrahydrofuran for 8 hours gave **9a** in 50% yield (Scheme 2). Treatment of **3b-h** with *p*-toluenesulfonic acid in boiling ethanol afforded the corresponding pyrimidino[1,6-*a*]-benzimidazoles **9a-h** in good yields (Scheme 1, Table V and VI). It is worth noting that refluxing of **3i** with *p*-toluenesulfonic acid under the same conditions afforded

Scheme 2



2-(3-aminopyrazol-4-yl)benzimidazole (**11**) in 80% yield, which was also obtained upon heating of **1** with hydrazine hydrate in ethanol (Scheme 2). In the ir spectrum of **11**, no absorption band in nitrile region was observed, and the ^{1}H-nmr spectrum of **11** was consistent with the proposed structure. Similar treatment of **3j** with *p*-toluenesulfonic acid gave a mixture of 2-anilinopyrimidino[1,6-*a*]benzimidazol-1(2*H*)-one-4-carbonitrile (**9j**) and 2-(5-amino-1-phenylpyrazol-4-yl)benzimidazole (**12**) in 17 and 25% yields, respectively (Scheme 2). The latter compound has been prepared from **1** and phenylhydrazine [2b].

On the basis of the above results, we propose a possible mechanism for the formation of **9** from **3** (Scheme 3). The *o*-amino group initially attacks at 4-position of pyrimidine nucleus in **3** to give spiro-intermediate **13** which is readily converted to **14** and the recyclization of **14** gives **9**, with loss of ammonia. Analogous cleavage of pyrimidine ring has been described for ethyl 4-(2-aminoanilino)pyrimidine-5-carboxylate in acid [9]. In the formation of 2-(pyrazolyl)-benzimidazole **11**, intramolecular cyclization between the cyano group and the hydrazino group of an intermediate **15** predominantly gives a pyrazole ring compound **16**, which is hydrolyzed to **11**. In the case of an intermediate **14** (R = NHC_6H_5) generated from **3j**, the above two orientations of cyclization are competitive to give simultaneously **9j** and **12** because of the phenyl group substituted at the hydrazino moiety.

In conclusion, the present work provides novel and convenient methods which are applicable to the preparation of a variety of 3-substituted pyrimidino[4,5-*b*]benzodiazepin-2-ones **8** and 2-substituted pyrimidino[1,6-*a*]benzimidazol-1-ones **9**.

Scheme 3

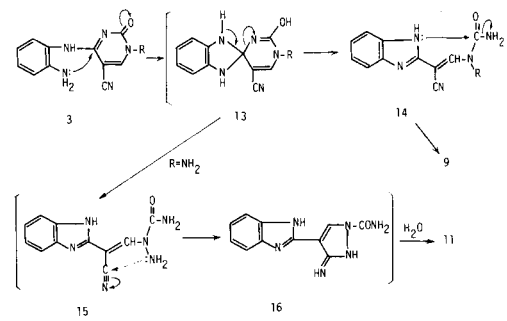


Table IV

Spectral Data for Compounds **8a-j**

Compound No.	IR (cm^{-1}) KBr	MS m/z	^{1}H-NMR (ppm) DMSO-d_6
8a	3350, 3270, 1640	241	3.33 (s, 3H), 4.0-9.4 (br, 3H), 6.57-7.27 (m, 4H), 8.15 (s, 1H)
8b	3420, 3360, 1640	225	1.27 (t, J = 8 Hz, 3H), 3.80 (q, J = 8 Hz, 2H), 6.63-7.20 (m, 4H), 6.3-8.7 (br, 3H), 8.17 (s, 1H)
8c	3380, 1630	269	0.87 (t, J = 7 Hz, 3H), 1.37-2.00 (m, 2H), 3.70 (t, J = 8 Hz, 2H), 6.67-7.00 (m, 4H), 6.7-7.8 (br, 3H), 8.10 (s, 1H)
8d	3475, 3440, 1640	269	1.32 (d, J = 7 Hz, 6H), 4.63 (hep, J = 7 Hz, 1H), 5.6-8.3 (br, 3H), 6.57-7.10 (m, 4H), 7.97 (s, 1H)
8e	3420, 1640	283	0.73-2.03 (m, 7H), 3.78 (t, J = 7 Hz, 2H), 6.67-7.13 (m, 4H), 6.6-8.7 (br, 3H), 8.15 (s, 1H)
8f	3360, 1635	267	4.43 (d, J = 6 Hz, 2H), 5.03-6.37 (m, 3H), 6.77-7.20 (m, 4H), 6.5-8.5 (br, 3H), 8.10 (s, 1H)
8g	3440, 1650	309	0.87-2.00 (m, 10H), 4.00-4.53 (m, 1H), 6.70-7.03 (m, 4H), 6.6-8.0 (br, 3H), 8.00 (s, 1H)
8h	3420, 1635	317	4.97 (s, 2H), 6.63-7.00 (m, 4H), 6.3-7.9 (br, 3H), 7.33 (s, 5H), 8.30 (s, 1H)
8i	3440, 1665	242	5.78 (s, 2H), 6.83-7.02 (m, 4H), 6.4-7.7 (br, 3H), 8.08 (s, 1H)
8j	3420, 3330, 1670	318	4.5-8.1 (br, 3H), 6.57-7.42 (m, 9H), 8.17 (s, 1H), 9.03 (s, 1H)

Table V

Physical Data for Compounds **9a-h** and **9j**

Compound No.	R	Yield %	Mp °C	Molecular Formula	Analyses Calcd. % Found % C	H	N
9a	CH_3	69	> 300	$C_{12}H_8N_4O$	64.24	3.60	24.99
				(224.22)	64.19	3.54	25.10
9b	C_2H_5	80	270-271	$C_{13}H_{10}N_4O$	65.54	4.23	23.52
				(238.25)	65.48	4.24	23.56
9c	*n*-C_3H_7	79	230-231	$C_{14}H_{12}N_4O$	66.66	4.79	22.21
				(252.28)	66.71	4.71	22.37
9d	*iso*-C_3H_7	90	282-283	$C_{14}H_{12}N_4O$	66.66	4.79	22.21
				(252.28)	66.45	4.74	22.29
9e	*n*-C_4H_9	71	179-181	$C_{15}H_{14}N_4O$	67.64	5.30	21.04
				(266.31)	67.51	5.32	20.89
9f	$CH_2CH=CH_2$	80	225-226	$C_{14}H_{10}N_4O$	67.19	4.03	22.39
				(250.26)	66.81	3.99	22.38
9g	C_6H_{11}	83	268-269	$C_{17}H_{16}N_4O$	69.84	5.52	19.17
				(292.34)	69.48	5.50	19.12
9h	CH_2-Ph	94	200-201	$C_{18}H_{12}N_4O$	71.99	4.03	18.66
				(300.32)	71.72	4.09	18.51
9j	NH-Ph	17	256-261	$C_{17}H_{11}N_5O$	67.77	3.68	23.24
				(301.31)	67.47	3.51	23.49

Table VI

Spectral Data for Compounds **9a-h** and **9j**

Compound No.	IR (cm^{-1}) KBr	MS m/z	^{1}H-NMR (ppm) CF_3CO_2D [a]
9a	2240, 1715	224	3.97 (s, 3H), 7.63-8.10 (m, 3H), 8.53-8.90 (m, 1H), 8.78 (s, 1H)
9b	2220, 1710	238	1.65 (t, J = 7 Hz, 3H), 4.48 (q, J = 7 Hz, 2H), 7.67-8.10 (m, 3H), 8.63-9.03 (m, 1H), 8.83 (s, 1H)
9c	2220, 1710	252	1.10 (t, J = 8 Hz, 3H), 1.67-2.27 (m, 2H), 4.30 (t, J = 7 Hz, 2H), 7.67-8.00 (m, 3H), 8.50-8.74 (m, 1H), 8.73 (s, 1H)
9d	2220, 1705	252	1.70 (d, J = 7 Hz, 6H), 5.33 (hep, J = 7 Hz, 1H), 7.77-8.00 (m, 3H), 8.60-8.93 (m, 1H), 8.83 (s, 1H)
9e	2230, 1710	266	0.80-2.32 (m, 7H), 4.40 (t, J = 7 Hz, 2H), 7.60-8.15 (m, 3H), 8.53-8.97 (m, 1H), 8.82 (s, 1H)
9f	2230, 1715	250	4.97 (d, J = 7 Hz, 2H), 5.40-6.37 (m, 3H), 7.70-8.10 (m, 3H), 8.53-8.87 (m, 1H), 8.77 (s, 1H)
9g	2250, 1710	292	1.27-2.40 (m, 10H), 4.63-5.17 (m, 1H), 7.77-8.00 (m, 3H), 8.60-8.93 (m, 1H), 8.83 (s, 1H)
9h	2210, 1710	300	5.40 (s, 2H), 7.40 (s, 5H), 7.63-8.00 (m, 3H), 8.50-8.80 (m, 1H), 8.60 (s, 1H)
9j	3310, 2230, 1720	301	6.62-8.35 (m, 9H), 8.87 (s, 1H), 9.42 (s, 1H)

[a] Measured in DMSO-d_6 solution for **9j**.

EXPERIMENTAL

Melting points were determined using a Yanagimoto micro melting point apparatus and are uncorrected. Infrared (ir) spectra were recorded from potassium bromide discs on a JASCO A-102 spectrophotometer. Nuclear magnetic resonance (^{1}H-nmr) spectra were measured with a JNM-PMX 60 spectrometer (JEOL) with tetramethylsilane as an internal standard. Mass spectra (ms) were taken on a JMS-DX 300 spectrometer (JEOL). Elementary analyses were performed on a Perkin-Elmer model 240B machine.

4-Ethoxycarbonylamino-1,5-benzodiazepine-3-carbonitrile (**2**).

Ethyl chloroformate (13.0 g, 0.12 mole) was added dropwise to a suspension of **1** (18.4 g, 0.1 mole) in ethanol (200 ml) containing triethylamine (10.1 g, 0.1 mole) with stirring at about 0°. The stirring was then continued for 0.5 hour at room temperature. The precipitate was collected, washed with ethanol and recrystallized from DMF/ethanol to yield **2** (19.2 g, 75%) as deep red crystals, mp 240° dec; ir: 3270, 3220, 2200, 1660 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 1.27 (t, J = 8 Hz, 3H), 4.18 (q, J = 8 Hz, 2H), 6.50-7.33 (m, 4H), 6.5-7.4 (br, 1H), 7.23 (s, 1H), 10.71 (br s, 1H); ms [FAB(+)] m/z 257 $(M+H)^+$.

Anal. Calcd. for $C_{13}H_{12}N_4O_2$: C, 60.93; H, 4.72; N, 21.87. Found: C, 60.74; H, 4.70; N, 21.57.

1-Substituted 4-(2-aminoanilino)pyrimidin-2(1*H*)-one-5-carbonitriles **3a-i**.

General Procedure.

A mixture of **2** (1.28 g, 5 mmoles) and an aliphatic primary amine (7.5 mmoles) in ethanol (20 ml) was stirred at room temperature for 24 hours. The precipitate was collected by suction filtration, washed with ethanol and recrystallized from appropriate solvent to yield **3a-h**. Similar treatment of **2** with hydrazine hydrate in ethanol for 3 hours gave **3i**. The data for these compounds are given in Table I and II.

2-(2'-Anilino-1'-cyanovinyl)benzimidazole (**5**).

Method A.

A mixture of **2** (0.51 g, 2 mmoles) and aniline (0.93 g, 10 mmoles) in

ethanol (10 ml) was refluxed for 3 hours. After cooling, the precipitate was collected by suction filtration and recrystallized from ethanol to yield **5** (0.35 g, 67%), mp 246-248°; ir: 3220, 2220, 1635 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 6.85-7.97 (m, 9H), 8.50 (d, J_{NH-CH} = 11 Hz, 1H), 12.16 (s, 1H), 12.45 (br s, 1H); ms: m/z 260 (M^+).

Anal. Calcd. for $C_{16}H_{12}N_4$: C, 73.83; H, 4.65; N, 21.53. Found: C, 73.48; H, 4.65; N, 21.53.

Method B.

A mixture of hydrochloride of **1** (1.10 g, 5 mmoles) and aniline (10 ml) was heated at 90-95° for 15 minutes. After cooling, methanol (15 ml) was added to the reaction mixture. The precipitate was collected, washed with methanol and recrystallized from ethanol to yield **5** (0.45 g, 35%).

2-[1′-Cyano-2′-(*p*-methoxyanilino)vinyl]benzimidazole (**6**).

Treatment of **2** (0.51 g, 2 mmoles) with *p*-anisidine (1.23 g, 10 mmoles) in ethanol (10 ml) in the same manner as described for the formation of **5** from **2** and aniline gave **6** (0.23 g, 40%), mp 212-214° (ethanol); ir: 3350, 2210 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 3.40 (s, 3H), 6.,92-7.86 (m, 9H), 8.45 (d, J_{NH-CH} = 11 Hz, 1H), 12.31 (br s, 1H), 12.54 (s, 1H); ms: m/z 290 (M^+), 275 (M^+-CH_3).

Anal. Calcd. for $C_{17}H_{14}N_4O$: C, 70.33; H, 4.86; N, 19.30. Found: C, 69.98; H, 4.84; N, 19.25.

Ring-opened Adduct **7** from **2** and Phenylhydrazine.

A mixture of **2** (1.0 g, 4 mmoles) and phenylhydrazine (0.9 g, 8 mmole) in ethanol (15 ml) was stirred at room temperature for 24 hours. The precipitate was collected, washed with ethanol and recrystallized from DMF/ethanol to yield **7** (1.04 g, 71%), mp 170-172°; ir: 3450, 3370, 3280, 3250, 2190, 1705 cm^{-1}; ^{1}H-nmr (DMSO-d_6-deuterium oxide): δ 1.10 (1.21) (t, J = 7 Hz, 3H), 3.98 (4.09) (q, J = 7 Hz, 2H), 6.81 (m, 9H), 7.51 (7.61) (s, 1H); ms: m/z 364 (M^+), 275 (M^+-$NH_2CO_2C_2H_5$).

Anal. Calcd. for $C_{19}H_{20}N_6O_2$: C, 62.62; H, 5.53; N, 23.06. Found: C, 62.55; H, 5.53; N, 22.92.

Cyclization of **7** into **3j**.

A mixture of **7** (1.1 g, 3 mmoles) and triethylamine (1 ml) in ethanol (10 ml) was refluxed for 2 hours. After cooling, the precipitate was collected, washed with ethanol and recrystallized from DMF/ethanol to yield **3j** (0.66 g, 69%), mp 179-181°; ir: 3275, 2130, 1670 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 4.6-8.1 (br, 3H), 6.30-7.38 (m, 9H), 8.73 (s, 1H), 9.00 (s, 1H); ms: m/z 318 (M^+), 275 (M^+-HNCO).

Anal. Calcd. for $C_{17}H_{14}N_6O$: C, 64.14; H, 4.43; N, 26.40. Found: C, 63.87; H, 4.25; N, 26.68.

3-Substituted 5-Aminopyrimidino[4,5-*b*][1,5]benzodiazepin-2(3*H*,11*H*)-ones **8a-j**.

General Procedure.

A mixture of **3a-j** (3 mmoles) and triethylamine (1.0 g, 10 mmoles) in ethanol (20 ml) was refluxed for 72 hours. After cooling, the precipitate was collected by suction filtration, washed with ethanol and dried in a vacuum desicator to yield **8a-j**. The data for these compounds were listed in Tables III and IV.

2-Substituted Pyrimidino[1,6-*a*]benzimidazol-1(2*H*)-one-4-carbonitriles **9a-h**.

General Procedure.

A mixture of **3a-h** (4 mmoles) and *p*-toluenesulfonic acid (2.1 g, 12 mmoles) in ethanol (30 ml) was refluxed for 3 hours. Evaporation of the solvent *in vacuo* gave a residue, which was recrystallized from ethanol (**9e**) or DMF/ethanol (**9a-d** and **9f-h**). The data for these compounds were given in Tables V and VI.

Reaction of **3a** with 1,4-Diazabicyclo[2.2.2]octane (DABCO).

A mixture of **3a** (0.48 g, 2 mmoles) and DABCO (1.12 g, 10 mmoles) in ethanol (10 ml) was refluxed for 40 hours. After cooling, the precipitate was collected by filtration, washed with ethanol and recrystallized from DMF/ethanol to yield **9a** (0.14 g, 22%), mp >300°. The filtrate was poured into water and the precipitate was collected, washed with water and recrystallized from ethanol to yield 2-(1′-cyano-2′-methylaminovinyl)-imidazole (**10**) (0.13 g, 23%), mp 225-226°; ir: 3310, 2210 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 3.20 (d, J = 4 Hz, 3H), 6.93-7.97 (m, 4H), 7.50 (d, J_{NH-CH} = 13 Hz, 1H), 9.6-10.3 (br, 1H), 12.19 (br s, 1H); ms: m/z 198 (M^+).

Anal. Calcd. for $C_{11}H_{10}N_4$: C, 66.65; H, 5.09; N, 28.27. Found: C, 66.58; H, 5.08; N, 28.43.

Synthesis of **9a** from **10**.

A solution of **10** (0.10 g, 0.5 mmole) and *N,N′*-carbonyldiimidazole (Im_2CO) (0.49 g, 3 mmoles) in tetrahydrofuran (5 ml) was refluxed for 8 hours. After removal of the solvent *in vacuo*, the residue was treated with chloroform to yield a crystalline solid. Recrystallization from DMF/ethanol afforded **9a** (56 mg, 50%), mp >300°, which was identified by comparison of its ir spectrum with that of **9a** obtained by treatment of **3a** with *p*-toluenesulfonic acid in ethanol.

2-(3-Aminopyrazol-4-yl)benzimidazole (**11**).

Method A.

A mixture of **3i** (0.73 g, 3 mmoles) and *p*-toluenesulfonic acid (1.55 g, 9 mmoles) in ethanol (20 ml) was refluxed for 2.5 hours. After cooling, the precipitate was collected, washed with ethanol and dissolved in water. The resulting solution was made alkaline with sodium carbonate to give a crystalline precipitate which was collected, washed with water and recrystallized from ethanol/water to yield **11** (0.48 g, 80%), mp 292-294° dec; ir: 3440, 3320, 3200, 1630, 1605 cm^{-1}; ^{1}H-nmr (DMSO-d_6): δ 5.85 (br s, 2H), 6.90-7.67 (m, 4H), 7.92 (s, 1H), 11.4-12.9 (br, 2H); ms: m/z 199 (M^+).

Anal. Calcd. for $C_{10}H_9N_5$: C, 60.29; H, 4.55; N, 35.16. Found: C, 59.96; H, 4.50; N, 35.16.

Method B.

A mixture of **1** (0.55 g, 3 mmoles) and hydrazine hydrate (0.45 g, 9 mmoles) in ethanol (15 ml) was refluxed for 7 hours. The reaction mixture was concentrated *in vacuo* and the residue was recrystallized from ethanol/water to yield **11** (0.4 g, 67%).

Formation of **9j** and **12** from **3j**.

A mixture of **3j** (0.64 g, 2 mmoles) and *p*-toluenesulfonic acid (1.1 g, 6 mmoles) in ethanol (15 ml) was refluxed for 2.5 hours. After removal of the solvent *in vacuo*, the residue was triturated in a sodium carbonate solution, and the whole was extracted with ethyl acetate. The organic layer was washed with water, dried over anhydrous sodium sulfonate and concentrated to give a residue which was then treated with a small amount of ethanol. The insoluble solid was collected by suction filtration and recrystallized from DMF/ethanol to give **9j** (0.1 g, 17%). The data for this compound are given in Table V and VI. The ethanolic filtrate was concentrated *in vacuo* and the residue was recrystallized from ethanol/water to yield **12** (0.14 g, 25%), mp 218-220° dec, which was identified by comparison of its ir spectrum with that of the authentic sample (lit [2b] mp 212-214°) obtained from **1** and phenylhydrazine.

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