Novel Ring Transformations of 4-Acylamino- and 4-Dimethylaminomethyleneamino-1*H*-1,5-benzodiazepine-3-carbonitriles to Pyrimidine-5-carbonitriles

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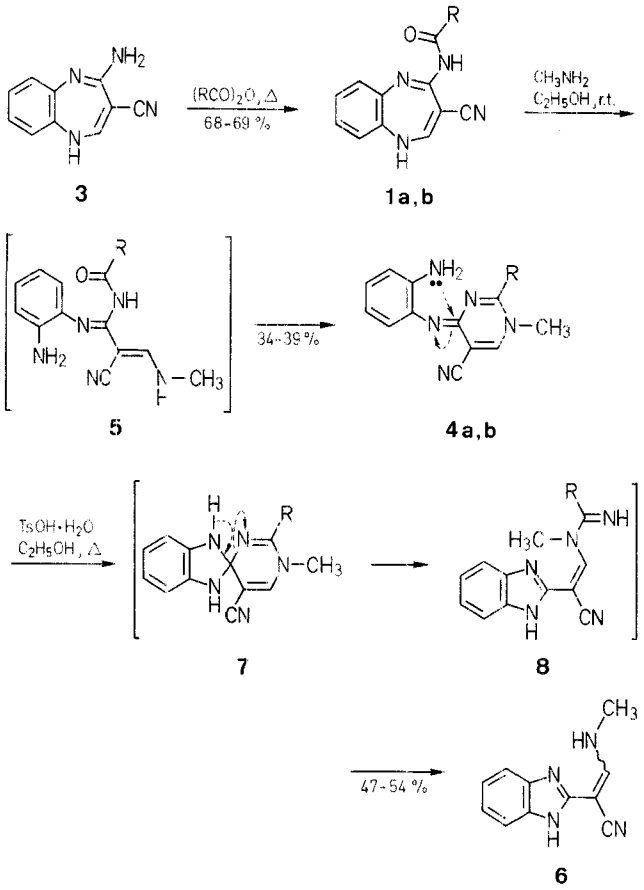
Reaction of 4-acylamino-1*H*-1,5-benzodiazepine-3-carbonitriles **1** with methylamine gave 2-alkyl-4-(*o*-aminophenylimino)-1-methyl-1,4-dihydropyrimidine-5-carbonitriles **4**. 4-Dimethylaminomethyleneamino-1*H*-1,5-benzodiazepine-3-carbonitrile **2** also underwent analogous ring transformation with methylamine and ammonia to give pyrimidine-5-carbonitriles **9** and **10**. The pyrimidines so formed were converted to benzimidazoles **6** and **12**.

Previously we reported[1,2] the ring transformation of 4-ethoxycarbonylamino-1*H*-1,5-benzodiazepine-3-carbonitrile with aliphatic primary amines to give cytosine derivatives which were useful key intermediates for the formation of pyrimido[4,5-*b*][1,5]benzodiazepine and pyrimido[1,6-*a*]benzimidazole ring systems. As an extension of this work, we now report that 4-acylamino-1*H*-1,5-benzodiazepine-3-carbonitriles **1** and 4-dimethylaminomethyleneamino-1-*H*-1,5-benzodiazepine-3-carbonitrile **(2)** undergo a similar ring transformation on reaction with an aliphatic amine and ammonia. The resultant pyrimidine-5-carbonitriles are further converted to benzimidazoles when heated in the presence of *p*-toluenesulfonic acid.

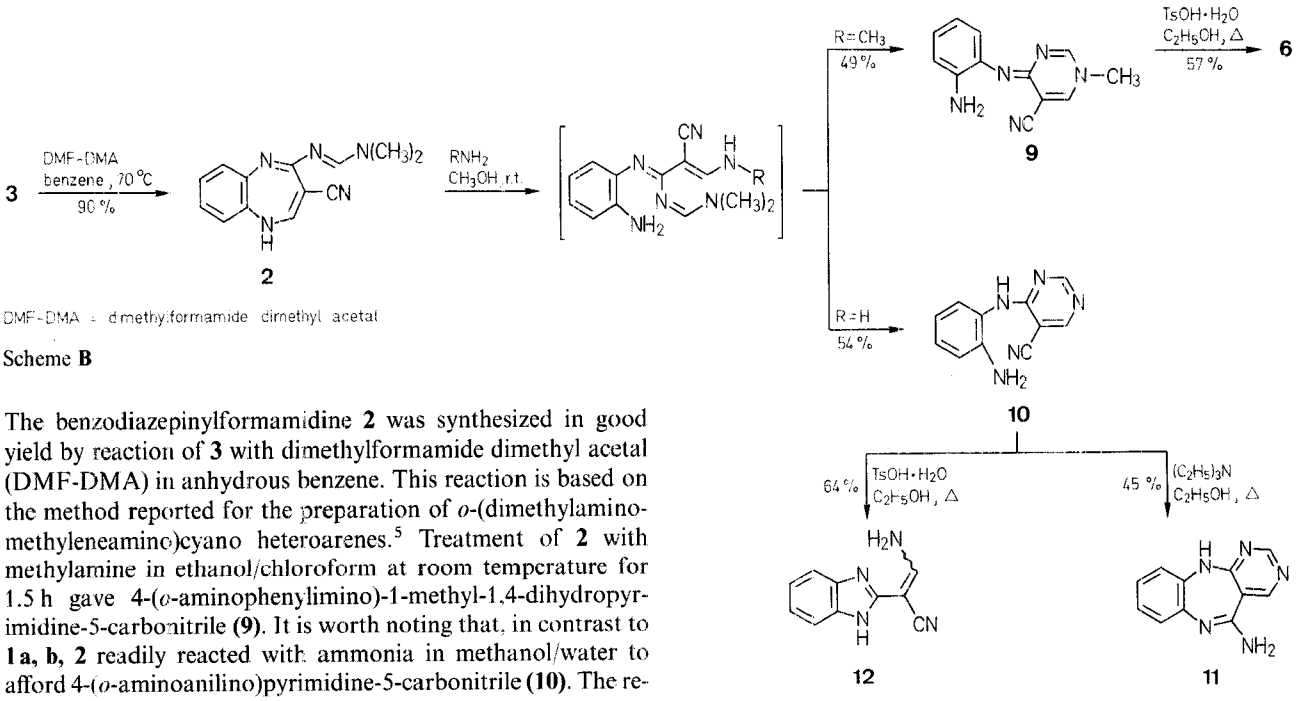
The 4-acylamino-benzodiazepines **1a, b** were readily synthesized on heating 4-amino-1*H*-1,5-benzodiazepine-3-carbonitrile **(3)**[3] with an acid anhydride without solvent. The structures of **1a, b** were determined on the basis of spectral data. In particular, the ^{1}H-NMR spectra of **1a, b** showed a broad singlet signal (**1a**: $\delta = 10.83$ ppm, **1b**: $\delta = 11.38$ ppm) which could be attributable to one amido proton. This observation indicates that the acylation took place selectively on the 4-amino group of **3**, but not on the nitrogen atom in the diazepine nucleus. When a suspension of **1a, b** in ethanol was stirred with an excess of methylamine at room temperature for 24 h, 2-alkyl-4-(*o*-aminophenylimino)-1-methyl-1,4-dihydropyrimidine-5-carbonitriles **4a, b** were obtained. The structural assignement of **4a, b** is based on microanalyses, and on mass, IR and ^{1}H-NMR spectral data. The reaction involves initial attack of methylamine at 2-position of **1** to afford the ring-opened intermediates **5**, followed by liberation of water from **5** to give **4** (Scheme **A**). The pyrimidines **4a, b** did not undergo intramolecular cyclization to pyrimido[4,5-*b*][1,5]benzodiazepines on treatment with triethylamine, although analogous 4-(*o*-aminoanilino)pyrimidine-5-carbonitriles afforded the corresponding tricyclic benzodiazepines.[1] These results are consistent with an imine structure possessing the *anti* configuration, which does not allow the *o*-amino group to interact with the cyano group. This is in contrast to compounds such as 4-(*o*-aminoanilino)pyrimidine-5-carbonitrile **(10)**, in which ring closure can readily occur. On the other hand, heating of **4a, b** with *p*-toluenesulfonic acid in ethanol resulted in the formation of 2-(1-cyano-2-methylaminovinyl)benzimidazole **(6)**.[2] The reaction mechanism is shown in Scheme **A**, where **4a, b** might cyclize to a spiro intermediate **7**, followed by ring opening to give **(8)** which was hydrolyzed to **6**. Similar cleavage of the pyrimidine ring has been described for ethyl 4-(*o*-aminoanilino)pyrimidine-5-carboxylate in acid.[4]



TsOH = *p*-toluenesulfonic acid

	R
a	CH_3
b	C_2H_5

Scheme **A**



DMF-DMA = dimethylformamide dimethyl acetal

Scheme **B**

The benzodiazepinylformamidine **2** was synthesized in good yield by reaction of **3** with dimethylformamide dimethyl acetal (DMF-DMA) in anhydrous benzene. This reaction is based on the method reported for the preparation of *o*-(dimethylaminomethyleneamino)cyano heteroarenes.[5] Treatment of **2** with methylamine in ethanol/chloroform at room temperature for 1.5 h gave 4-(*o*-aminophenylimino)-1-methyl-1,4-dihydropyrimidine-5-carbonitrile (**9**). It is worth noting that, in contrast to **1a, b, 2** readily reacted with ammonia in methanol/water to afford 4-(*o*-aminoanilino)pyrimidine-5-carbonitrile (**10**). The reaction mechanisms for the formation of **9** and **10** are represented in Scheme **B**. Intramolecular cyclization of **10** to 5-amino-1*H*-pyrimido[4,5-*b*][1,5]benzodiazepine (**11**) was accomplished on refluxing with triethylamine in ethanol, whereas similar attempt at **9** failed as in the case of **4a, b**. The pyrimidines **9** and **10** were converted into benzimidazoles **6** and **12**, respectively, on heating with *p*-toluenesulfonic acid in ethanol. These acid-catalysed rearrangement can be explained by a similar mechanism as proposed for the formation of **6** from **4**.

4-Acylamino-1*H*-1,5-benzodiazepine-3-carbonitriles 1a, b:
A mixture of **3** (0.92 g, 5 mmol) and acetic anhydride or propionic anhydride (10 mmol) is heated on a water bath for 15 min. After cooling, the reaction mixture is treated with ethanol (30 ml) to give a crystalline solid which is collected, washed with ethanol and recrystallized from dimethylformamide/ethanol to yield **1a** or **1b** (Table).

4-Dimethylaminomethyleneamino-1*H*-1,5-benzodiazepine-3-carbonitrile (2):
A mixture of **3** (3.7 g, 20 mmol) and DMF-DMA (3 ml) in anhydrous benzene (10 ml) is heated at 70 °C for 15 min with stirring. After cooling, the precipitate is collected by suction and recrystallized from ethyl acetate/ethanol; yield: 4.3 g (90%); m.p. 150–152 °C.

$C_{13}H_{13}N_5$ (239.3) calc. C 65.25 H 5.48 N 29.27
found 65.46 5.47 29.55

IR (KBr): ν = 3270, 2220 cm^{-1}.

^{1}H-NMR (DMSO-d_6): δ = 2.93 (s, 3H, CH_3); 3.10 (s, 3H, CH_3); 6.25–6.90 (m, 5 H_{arom} and =CH); 7.5–8.9 (br, 1H, NH); 8.25 ppm (s, 1H, =CH).

MS: m/e = 239 (M^+).

2-Alkyl-4-(*o*-aminophenylimino)-1-methyl-1,4-dihydropyrimidine-5-carbonitriles 4a, b:
A mixture of **1a, b** (3 mmol) and methylamine (0.5 ml of 30% ethanolic solution) in ethanol (10 ml) is stirred at room temperature for 24 h. The precipitate is collected by suction and recrystallized from dimethylformamide/ethanol to yield **4a, b** (Table).

2-(1-Cyano-2-methylaminovinyl)benzimidazole (6):
A mixture of a pyrimidine (**4a, b** or **9**, 1.5 mmol) and *p*-toluenesulfonic acid monohydrate (0.86 g, 4.5 mmol) in ethanol (10 ml) is refluxed for 2 h. The reaction mixture is concentrated *in vacuo* and the residue is treated with 10% sodium carbonate solution (15 ml). The precipitate is collected and purified by column chromatography on silica gel (20 g)

Table. 4-Acylaminobenzodiazepines **1a, b** and Pyrimidine-5-carbonitriles **4a, b, 9** and **10** Prepared

Product	Yield (%)	m.p.[a] (°C)	Molecular Formula[b]	MS[c] *m/e* (M^+)	^{1}H-NMR (DMSO-d_6)[d] δ (ppm)
1a	68	220–224 (dec.)	$C_{12}H_{10}N_4O$ (226.2)	226	2.12 (s, 3H, CH_3); 6.23–7.42 (m, 4H_{arom}); 7.11 (s, 1H, =CH); 8.7–10.2 (br, 1H, NH); 10.83 (br s, 1H, NHCO)
1b	69	203–206 (dec.)	$C_{13}H_{12}N_4O$ (240.3)	240	0.99 (t, 3H, J = 7 Hz, CH_3); 2.30 (q, 2H, J = 7 Hz, $-CH_2-$); 6.22–7.15 (m, 4H_{arom}); 6.95 (s, 1H, =CH); 9.0–10.3 (br s, 1H, NH); 11.38 (br s, NHCO)
4a	39	200–202 (dec.)	$C_{13}H_{13}N_5$ (239.3)	239	2.17 (s, 3H, C–CH_3); 3.30 (s, 3H, N–CH_3); 4.49 (s, 2H, NH_2); 6.13–7.35 (m, 4H_{arom}); 7.91 (s, 1H, =CH)
4b	34	190–194 (dec.)	$C_{14}H_{15}N_5$ (253.3)	253	1.07 (t, 3H, J = 7 Hz, CH_3); 2.55 (q, 2H, J = 7 Hz, $-CH_2-$); 3.41 (s, 3H, N–CH_3); 4.71 (s, 2H, NH_2); 6.27–7.73 (m, 4H_{arom}); 8.12 (s, 1H, =CH)
9	49	150–152	$C_{12}H_{11}N_5$ (225.3)	225	3.38 (s, 3H, CH_3); 4.52 (br s, 2H, NH_2); 6.23–7.20 (m, 4H_{arom}); 7.80 (d, 1H, J = 2 Hz, =CH); 8.02 (d, 1H, J = 2 Hz, =CH)
10	54	149–151	$C_{11}H_9N_5$ (211.2)	211	4.0–5.7 (br, 2H, NH_2); 6.22–7.28 (m, 4H_{arom}); 7.6–9.3 (br, 1H, NH); 8.40 (s, 1H, =CH); 8.48 (s, 1H, =CH)

[a] Melting points are uncorrected.
[b] Satisfactory microanalyses obtained: C ±0.30, H ±0.13, N ±0.28.
[c] Obtained on a JEOL JMS D-300 spectrometer.
[d] Obtained on a JEOL-C60H spectrometer in DMSO-d_6 solution.
[e] The IR spectra (KBr) showed the characteristic absorptions at 1640–1630 cm^{-1} (CO) and 2220–2200 cm^{-1} (CN) for **1a, b** and 2230–2220 cm^{-1} (CN) for **4a, b, 9** and **10**.

with chloroform (170 ml) as eluent. Recrystallization from ethanol gives **6**; yield: 0.16 g (54%) from **4a**, 0.14 g (47%) from **4b** and 0.17 g (57%) from **9**: m.p. 225–226°C (Lit.[2] m.p. 225–226°C).

4-(*o*-Aminophenylimino)-1-methyl-1,4-dihydropyrimidine-5-carbonitrile (9):
A mixture of **2** (0.48 g, 2 mmol) and methylamine (0.25 ml of 30% ethanolic solution) in chloroform (10 ml) is stirred at room temperature for 1.5 h. The reaction mixture is concentrated *in vacuo* and the residue is recrystallized from ethyl acetate/ethanol to afford **9**; yield: 0.22 g (49%) (Table).

4-(*o*-Aminoanilino)pyrimidine-5-carbonitrile (10):
A mixture of **2** (0.96 g, 4 mmol) and concentrated aqueous ammonia (5 ml) in methanol (5 ml) is stirred at room temperature for 30 min. The mixture is poured into water (50 ml) and extracted with ethyl acetate (3 × 20 ml). The organic layer is dried with anhydrous sodium sulfate and concentrated. The residual solid is recrystallized from ethyl acetate/ethanol; yield: 0.46 g (54%) (Table).

5-Amino-11*H*-pyrimido[4,5-*b*][1,5]benzodiazepine (11):
A mixture of **10** (0.42 g, 2 mmol) and triethylamine (1 ml) in ethanol (20 ml) is refluxed for 48 h. The mixture is concentrated *in vacuo*, and the residue is recrystallized from ethyl acetate/ethanol; yield: 0.19 g (45%); m.p. 249–252°C (dec.).

$C_{11}H_9N_5$	calc.	C 62.55	H 4.29	N 33.16
(211.2)	found	62.31	4.36	32.85

^{1}H-NMR (DMSO-d_6): δ = 4.4–9.2 (br, 3H, NH, NH_2); 6.63–7.03 (m, 4H_{arom}); 8.30 (s, 1H, =CH); 8.40 ppm (s, 1H, =CH).
MS: *m/e* = 211 (M^+).

2-(1-Cyano-2-aminovinyl)benzimidazole (12):
A mixture of **10** (0.32 g, 1.5 mmol) and *p*-toluenesulfonic acid monohydrate (0.86 g, 4.5 mmol) in ethanol (10 ml) is refluxed for 2 h. The mixture is concentrated *in vacuo* and the residue is treated with 10% sodium carbonate solution (15 ml). The precipitate is collected and recrystallized from ethanol; yield: 0.18 g (64%); m.p. 228–229°C.

$C_{10}H_8N_4$	calc.	C 65.21	H 4.38	N 30.42
(184.2)	found	65.52	4.39	30.13

IR (KBr): ν = 3320, 3160, 2200 cm^{-1}.
^{1}H-NMR (DMSO-d_6/TMS): δ = 6.74–7.90 (m, 5H_{arom} and =CH); 8.5–10.0 (br, 2H, NH_2); 11.68 ppm (s, 1H, NH).
MS: *m/e* = 184 (M^+).

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