# Conversion of 4-Amino-1*H*-1,5-benzodiazepine-3-carbonitrile to Pyrazolo[3,4-*d*]pyrimidines, Pyrimido[1,6-*a*]benzimidazole, and Pyrazolo[3',4':4,5]pyrimido[1,6-*a*]benzimidazoles [1]



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The reactions of multifunctional compounds **2a,b,c, 3a,b** and **4a,b** which were readily obtained from 4-amino-1*H*-1,5-benzodiazepine-3-carbonitrile **1** with orthoesters are described, and derivatives of pyrazolo-[3,4-*d*]pyrimidines **5**, pyrimido[1,6-*a*]benzimidazole **9**, and pyrazolo[3',4':4,5]pyrimido[1,6-*a*]benzimidazole **10** are synthesized.

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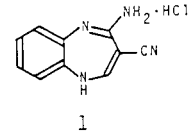
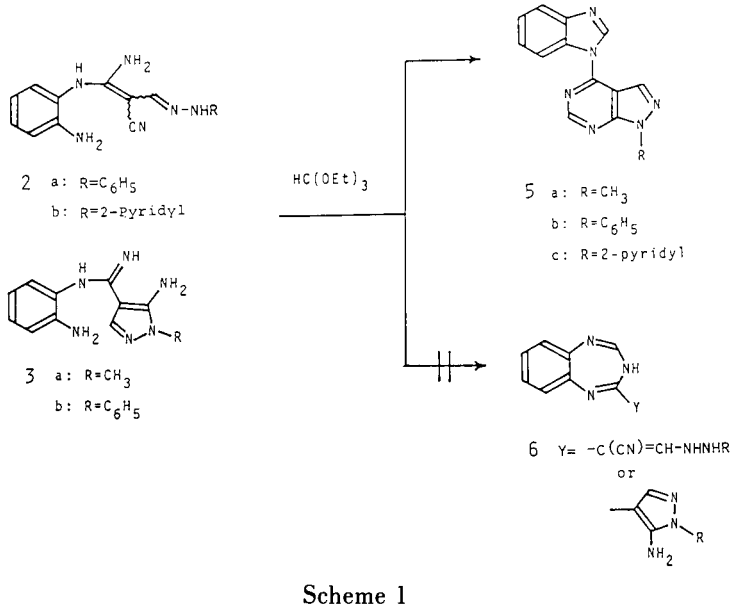
Recently, we have studied the ring transformations of 4-amino-1*H*-1,5-benzodiazepine-3-carbonitrile (**1**) with nucleophiles such as hydrazines and hydroxylamines [3,4], and those results have prompted us to examine the conversion of **1** to other heterocycles. In a previous paper, we tried to synthesize some heterocycles from multifunctional compounds **2** and its cyclized compounds **3** and **4** [5]. The results showed that both **2a** and **2b** were converted to mixtures of benzimidazoles and pyrazoles by the reaction with orthoesters (R' = H, $CH_3$, $C_2H_5$) in the presence of a protic solvent such as 1-butanol, and **2a** was reacted with orthoesters in benzene to give *N*-substituted benzimidazole derivatives which were readily degraded to benzimidazoles and pyrazoles by refluxing in 1-butanol. In this paper, we describe the reactions of **2, 3** and **4** with orthoesters without using solvent.

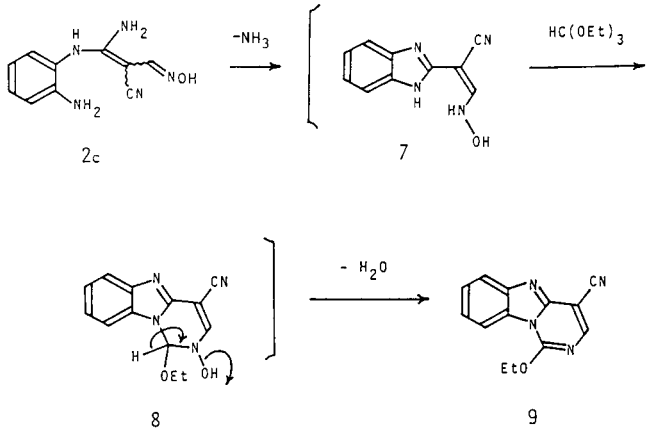
Refluxing of **2a,b** in triethyl orthoformate gave 1-substituted-4-(benzimidazol-1-yl)-1*H*-pyrazolo[3,4-*d*]pyrimidine derivatives **5b,c**, but not benzotriazepine derivative **6** (Scheme 1, Table I). Refluxing of **3a,b** in triethyl orthoformate also afforded **5a,b**. It is worth noting that the reaction of **3a**, as well as **2a** or **2b**, with orthoesters using 1-butanol as solvent gave mixtures of benzimidazole and pyrazole derivatives. On the other hand, refluxing of **2c** in triethyl orthoformate gave 9-cyano-2-ethoxy-pyrimido-[1,6-*a*]benzimidazole (**9**), but not a *N*-substituted benzimidazole. These results indicate that the multifunctional compounds **2a,b** initially formed pyrazole ring by intramolecular cyclization in triethyl orthoformate, followed by reaction with the orthoester to give **5a,b**. In fact, **2c** is not able to cyclize like **2a,b** in triethyl orthoformate, and therefore, the initiation of the reaction is different from that of **2a** or **2b**. The formation of **9** can be explained by



1



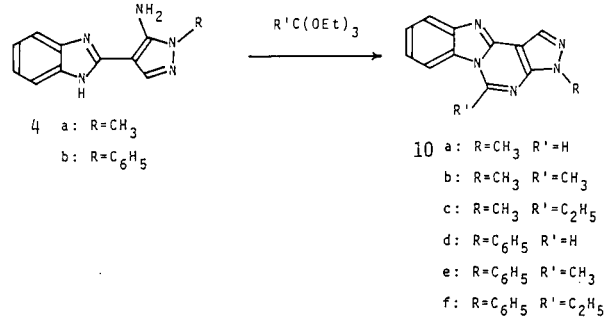

Scheme 1



Scheme 2

the removal of ammonia from **2c** to produce **7**, followed by the reaction with the orthoester to give **8** whose dehydration affords **9** (Scheme 2). Since many by-products (oily substances) were obtained when other orthoesters (R' = $CH_3$, $C_2H_5$) were utilized in the above reactions, only triethyl orthoformate was found to be useful.

The reactions of **4a,b** with orthoesters expectedly provided pyrazolo[3',4':4,5]pyrimido[1,6-*a*]benzimidazole derivatives **10** which may be regarded as derivatives of allopurinol, xanthine oxidase inhibitor [6], in a sense of imino substitution at the 4 position of its skeleton (Scheme 3, Table II). Interestingly, 1-butanol as the solvent sometimes was not effective even in these reactions. The starting material was recovered when **4a** was reacted with ethyl orthoacetate and ethyl orthopropionate in this solvent.



Scheme 3

Table I

Analytical Data of 1,4-Disubstituted-pyrazolo[3,4-*d*]pyrimidines **5**

| Compound | Mp (°C) | Yield % (S. M.) [a] | Formula | m/z ($M^+$) | Calcd./Found C | H | N |
|---|---|---|---|---|---|---|---|
| **5a** | 241-242 | 65 (**3a**) | $C_{13}H_{10}N_6$ | 250 | 62.39<br>62.15 | 4.03<br>4.02 | 33.58<br>33.33 |
| **5b** | 239-240 | 19 (**2a**)<br>37 (**3b**) | $C_{18}H_{12}N_6$ | 312 | 69.22<br>69.12 | 3.87<br>3.84 | 26.91<br>26.74 |
| **5c** | 250-251 | 62 (**2b**) | $C_{17}H_{11}N_7$ | 313 | 65.17<br>65.03 | 3.54<br>3.43 | 31.30<br>31.14 |

[a] Starting Material.

Table II

Analytical Data of Pyrazolo[3',4':4,5]pyrimido[1,6-*a*]benzimidazole Derivatives **10**

| Compound | Mp (°C) | Yield % | Formula | m/z ($M^+$) | Calcd./Found C | H | N |
|---|---|---|---|---|---|---|---|
| **10a** | 275-276 | 92 | $C_{12}H_9N_5$ | 223 | 64.56<br>64.41 | 4.06<br>3.98 | 31.38<br>31.03 |
| **10b** | 231-232 | 77 | $C_{13}H_{11}N_5$ | 237 | 65.81<br>65.73 | 4.67<br>4.81 | 29.52<br>29.41 |
| **10c** | 212-213 | 68 | $C_{14}H_{13}N_5$ | 251 | 66.91<br>66.87 | 5.21<br>5.32 | 27.87<br>27.80 |
| **10d** | >300 | 44 | $C_{17}H_{11}N_5$ | 285 | 71.56<br>71.86 | 3.89<br>3.86 | 24.55<br>24.70 |
| **10e** | 207-208 | 42 | $C_{18}H_{13}N_5$ | 299 | 72.22<br>72.19 | 4.38<br>4.30 | 23.40<br>23.33 |
| **10f** | 229-230 | 79 | $C_{19}H_{15}N_5$ | 313 | 72.82<br>72.52 | 4.83<br>4.72 | 22.35<br>22.38 |

## EXPERIMENTAL

Melting points were determined by using a Yamato Scientific stirred liquid apparatus and are uncorrected. Infrared (ir) and proton magnetic resonance (pmr) spectra (tetramethylsilane as internal standard) were recorded on a JASCO IR-G and Varian EM-90 spectrometers, respectively. The mass (ms) spectra were run on a JEOL 01S spectrometer. Elementary analyses were performed on a Perkin-Elmer 240B instrument.

4-(Benzimidazol-1-yl)-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (**5a**).

A solution of **3a** (0.2 g, 0.81 mmole) in 30 ml of triethyl orthoformate was refluxed on an oil-bath (150°) for 3 hours. After cooling to room temperature, precipitated crystals were filtered off, and dried to give 0.14 g of **5a**. The recrystallization solvent was acetic acid/water. Table I shows some physical constants of this compound; pmr (trifluoroacetic acid): δ 4.37 (3H, s, $CH_3$), 7.90 and 8.50 (4H, m, benzene ring), 8.77, 9.34, 10.00 (1H, s, respectively, other aromatic).

4-(Benzimidazol-1-yl)-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine (**5b**).

Method A.

A solution of **2a** (0.2 g, 0.68 mmoles) in 30 ml of triethyl orthoformate was refluxed on an oil-bath (150°) for 3 hours. After cooling to room temperature, the precipitate was filtered and dried, yield 19% (0.04 g), see Table I; pmr (deuteriochloroform): δ 7.34-8.70 (9H, m, benzene ring), 9.03, 9.07, 9.23 (1H, s, respectively, other aromatic).

Method B.

A solution of **3b** (0.5 g, 1.7 mmoles) in 30 ml of triethyl orthoformate was refluxed, and similar treatments gave **5b** in 37% (0.2 g) yield.

4-(Benzimidazol-1-yl)-1-(2-pyridyl)-1*H*-pyrazolo[3,4-*d*]pyrimidine (**5c**).

A solution of **2b** (0.2 g, 0.86 mmole) in 30 ml of triethyl orthoformate was refluxed for 4 hours, and similar treatment gave 0.13 g of **5c**. The recrystallization solvent was ethanol/chloroform; pmr (deuteriochloroform): δ 7.35-8.70 (8H, m, benzene + pyridine ring), 8.47, 8.73, 9.07 (1H, s, respectively, other aromatic).

9-Cyano-2-ethoxypyrimido[3,4-*a*]benzimidazole (**9**).

A solution of **2c** (0.2 g, 0.92 mmole) in 20 ml of triethyl orthoformate was refluxed on an oil-bath (150°) for 5 hours. The solvent was evaporated under a reduced pressure to give crystals which were filtered, washed with water, and dried to provide almost pure crystals of **9** in 50% yield (0.11 g), mp 232-233° (recrystallized from ethanol); ms: m/z 238 ($M^+$); ir: 2230 $cm^{-1}$ (C≡N); pmr (dimethylsulfoxide d-6): δ 1.42 (3H, t, $CH_3$), 4.62 (2H, q, $CH_2$), 7.50 (3H, m, aromatic), 8.25 (1H, d, 8-H), 9.92 (1H, s, 2-H).

*Anal.* Calcd. for $C_{13}H_{10}N_4O$: C, 65.54; H, 4.23; N, 23.52. Found: C, 65.37; H, 4.16; N, 23.46.

1-Methyl-1*H*-pyrazolo[3',4':4,5]pyrimido[1,6-*a*]benzimidazole (**10a**).

A solution of **4a** (0.5 g, 2.3 mmoles) in 30 ml of triethyl orthoformate was refluxed on an oil-bath (150°) for 1 hour. After cooling to room temperature, colorless crystals were precipitated, filtered off, and dried to provide 0.48 g of **10a**. Some analytical data are given in Table II; pmr (dimethylsulfoxide d-6): δ 4.13 (3H, s, $CH_3$), 7.50 (3H, m, benzene ring), 7.85 (1H, m, 8-H), 8.42 (1H, s, 3-H), 9.80 (1H, s, 10-H).

1,10-Dimethyl-1*H*-pyrazolo[3',4':4,5]pyrimido[1,6-*a*]benzimidazole (**10b**).

A solution of **4a** (0.2 g, 0.94 mmole) in 20 ml of triethyl orthoacetate was refluxed for 3 hours. The solution was condensed to become about a third volume by removal of the solvent under a reduced pressure to precipitate crystals which were filtered off, washed with water, and dried to give a pure **10b** in 77% yield (0.17 g). Some analytical data are listed in Table II; pmr (trifluoroacetic acid): δ 3.52 (3H, s, 10-$CH_3$), 4.37 (3H, s, 1-$CH_3$), 7.96 (3H, m, benzene ring), 8.45 (1H, m, 8-H), 8.90 (1H, s, 3-H).

10-Ethyl-1-methyl-1*H*-pyrazolo[3',4':4,5]pyrimido[1,6-*a*]benzimidazole (**10c**).

A solution of **4a** (0.2 g, 0.94 mmole) in 20 ml of triethyl orthopropionate was refluxed for 3 hours, and similar treatments described above provided pure crystals of **10c**. Some physical data are given in Table II; pmr (trifluoroacetic acid): δ 1.80 (3H, t, 10-$CH_3$), 3.83 (2H, q, 10-$CH_2$), 4.40 (1H, s, 1-$CH_3$), 7.96 (3H, m, benzene ring), 8.45 (1H, m, 8-H), 8.90 (1H, s, 3-H).

1-Phenyl-1*H*-pyrazolo[3',4':4,5]pyrimido[1,6-*a*]benzimidazole (**10d**).

A solution of **4b** (0.2 g, 0.37 mmole) in 30 ml of triethyl orthoformate was refluxed on an oil-bath (150°) for 7 hours. After cooling to room temperature, crystals were precipitated, filtered off, washed with water, and dried to provide pure **10d** in 44% yield (0.09 g). Some physical data are given in Table II; pmr (trifluoroacetic acid): δ 7.76 (8H, m, benzene ring), 8.33 (1H, m, 8-H), 9.00 (1H, s, 3-H), 9.67 (1H, s, 10-H).

10-Methyl-1-phenyl-1*H*-pyrazolo[3',4':4,5[pyrimido[1,6-*a*]benzimidazole (**10e**).

A mixture of **4b** (0.2 g, 0.73 mmole) and triethyl orthoacetate (1 g, 6.2 mmoles) in 30 ml of 1-butanol was refluxed on an oil-bath (150°) for 3 hours. After cooling to room temperature, crystals were precipitated, filtered off, washed with water, and dried to provide pure **10e** in 42% yield (0.09 g). Some analytical data are listed in Table II. The recrystallization solvent was ethanol/chloroform; pmr (deuteriochloroform): δ 3.10 (3H, s, 10-$CH_3$), 7.15-8.20 (9H, m, aromatic), 8.40 (1H, s, 3-H).

10-Ethyl-1-phenyl-1*H*-pyrazolo[3',4':4,5]pyrimido[1,6-*a*]benzimidazole (**10f**).

A mixture of **4b** (0.2 g, 0.73 mmole) and triethyl orthopropionate (1 g, 6.2 mmoles) in 30 ml of 1-butanol was refluxed on an oil-bath for 3 hours. After cooling to room temperature, crystals were precipitated, filtered off, washed with water, and dried to give pure **10f** in 79% yield (0.18 g). The recrystallization solvent was ethanol/chloroform. Some analytical data are listed in Table II; pmr (deuteriochloroform): δ 1.57 (3H, t, 10-$CH_3$), 3.38 (2H, q, 10-$CH_2$), 7.15-8.27 (9H, m, aromatic), 8.40 (1H, s, 3-H).

## REFERENCES AND NOTES

[1] This is Part IV in a series of "Ring Transformation of 4-Amino-1*H*-1,5-benzodiazepine-3-carbonitrile". Part III, see reference [5].

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