Synthesis of Pyrido[1′,2′:1,2]imidazo[4,5-*b*]pyrazines from 2-Amino-3-chloro-5,6-dicyanopyrazine with Substituted Pyridines

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Novel synthesis of the title compounds by the cyclization between 2-amino-3-chloro-5,6-dicyanopyrazine and various substituted pyridines is described.

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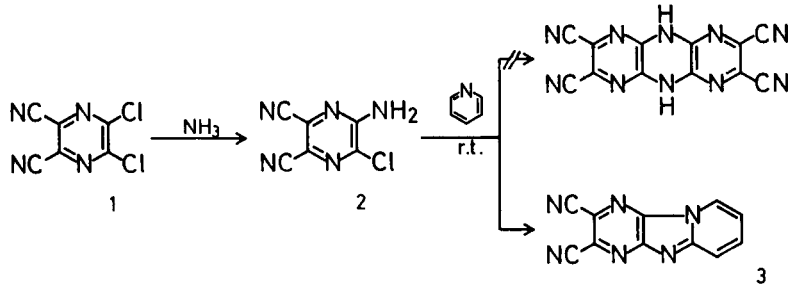
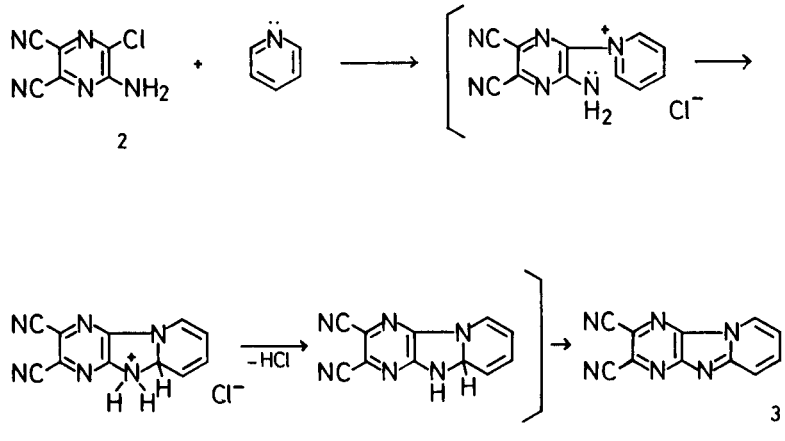
In the previous paper [1], we reported the synthesis of pyrido[1′,2′:1,2]imidazo[4,5-*b*]pyrazines bearing a bridgehead nitrogen atom at the 10-position by the facile cyclization between 2-aminopyridines and 2,3-dichloro-5,6-dicyanopyrazine (**1**). In the present paper, we also succeeded in the synthesis of the same nucleus *via* a different route of cyclization between substituted pyridines and 2-amino-3-chloro-5,6-dicyanopyrazine (**2**) which was prepared by controlled amination of **1**.

Recently, in the course of our attempt to prepare 2,3,6,7-tetracyano-1,4,5,8,9,10-hexaazaanthracene by self-condensation of **2** in pyridine as a solvent at room temperature, we have found that the substrate **2** reacted unexpectedly with pyridine to give 2,3-dicyanopyrido[1′,2′:1,2]-imidazo[4,5-*b*]pyrazine (**3**) (Scheme 1). The reaction was presumed to proceed by the shown mechanism (Scheme 2). In this mechanism, the lone pair of pyridine attacks first the electron deficient carbon bearing chlorine atom of the pyrazine **2**, giving a pyrazinopyridinium salt. An attempt to isolate the salt was unsuccessful and a successive neucleophilic attack of the amino group on the α-carbon of the pyridine nucleus occurred with elimination of hydrogen chloride. The resulting intermediate, which could not be isolated, is then oxidized somehow to yield the product **3**.

Scheme 1



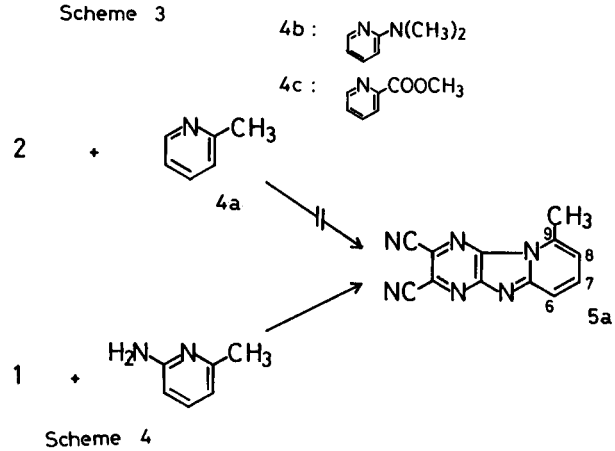
Scheme 2



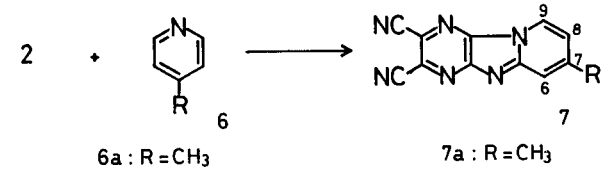
As an application of this reaction, the cyclization of various substituted pyridines with **2** was investigated. Structures of the products were determined by elemental analyses, ^{1}H-nmr and ir spectroscopy, and, in some cases, identified by comparison with authentic samples prepared by previously reported cyclization between 2-aminopyridines and **1**.

The reaction with 2-substituted pyridines such as 2-methylpyridine (**4a**), 2-dimethylaminopyridine (**4b**) and methyl 2-pyridinecarboxylate (**4c**) did not occur, recovering the substrate unreacted and no expected signal of the product (*e.g.* **5a**) could be observed with hplc (Scheme 3). It might be caused from steric hindrance, though the definite reason remains obscure. On the other hand, eight 4-substituted pyridines **6a-h** reacted readily with **2** to afford the corresponding 7-substituted products **7a-h** (Scheme 4). Only in the case of **6d**, oxidation might have followed the cyclization to give **7d**, which was identified by analytical and spectral studies. However, 4-cyano- (**6i**), 4-formyl- (**6j**) and 4-(*p*-toluoyl)pyridine (**6k**) were recovered unreacted, which suggests that the stronger electron withdrawing substituent on the pyridine nucleus inhibits the reaction similarly to our previous cyclization [1] of 2-aminopyridines with **1**.

Scheme 3



Scheme 4

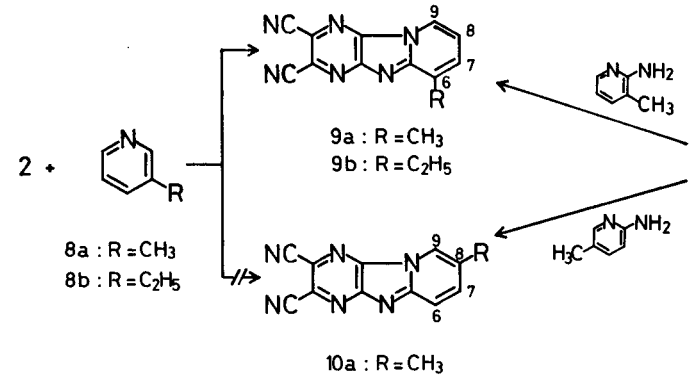


6a : R = CH_3
6b : R = n-C_3H_7
6c : R = tert-C_4H_9
6d : R = $CH_2C_6H_5$
6e : R = $CONH_2$
6f : R = $COOCH_3$
6g : R = C_6H_5
6h : R = 
6i : R = CN
6j : R = CHO
6k : R = COC_6H_4-p-CH_3

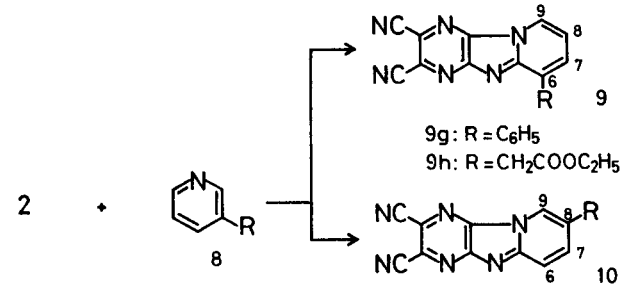
7a : R = CH_3
7b : R = n-C_3H_7
7c : R = tert-C_4H_9
7d : R = COC_6H_5
7e : R = $CONH_2$
7f : R = $COOCH_3$
7g : R = C_6H_5
7h : R = 

In the reaction with 3-substituted pyridines **8**, alternative directions in the ring closure are possible because of their structural dissymmetry. 3-Methylpyridine (**8a**) and 3-ethylpyridine (**8b**) cyclized with **2** preferentially at their 1,2-positions to afford the corresponding 6-substituted products **9a** and **9b**. No detectable amount of 8-substituted isomer (*e.g.* **10a**) was observed in ^{1}H-nmr and hplc by comparison with the authentic sample obtained previously by our method [1] (Scheme 5). In contrast, 3-pyridinecarboxamide (**8c**), methyl 3-pyridinecarboxylate (**8d**), 3,2′-bipyridyl (**8e**) and 3,3′-bipyridyl (**8f**) cyclized with **2** selectively at their 1,6-positions to give the corresponding 8-substituted products **10c-f** (Scheme 6). And 3-phenylpyridine (**8g**) and ethyl 3-pyridylacetate (**8h**) yielded a mixture of **9g-10g** and **9h-10h**, respectively. The stronger electron withdrawing substituent at the 3-position of the

Scheme 5



Scheme 6



8c : R = $CONH_2$
8d : R = $COOCH_3$
8e : R = 
8f : R =
8g : R = C_6H_5
8h : R = $CH_2COOC_2H_5$
8i : R = CN
8j : R = CHO
8k : R = $COCH_3$

Scheme 7

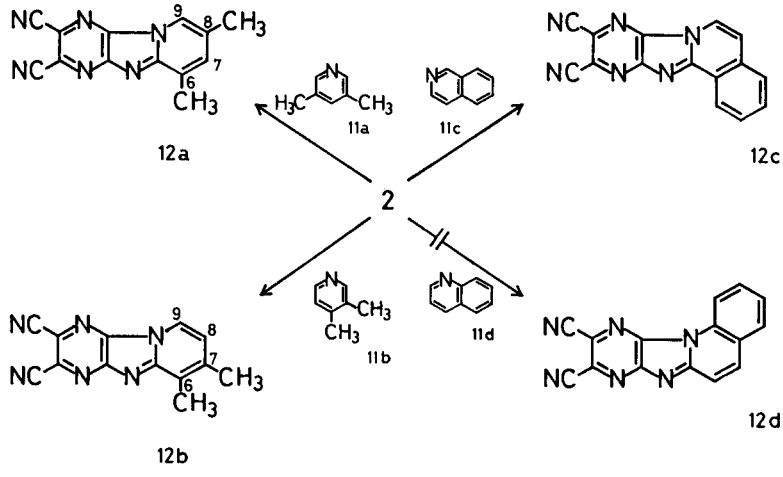


Table 1

Preparative and Physical Data for Products **3**, **7**, **9**, **10**, and **12**.

Product No.	Preparative Method	Recryst. Solvent	Yield (%)	Appearance	Mp (°C)
3	A	CH_3OH	73	yellow needles	316-318 dec (lit [1] 317-319 dec)
7a	A	CH_3OH	21	yellow needles	286-288 (lit [1] 286-288)
7b	B	C_6H_6	22	yellow needles	198-200
7c	B	CH_3OH	40	yellow needles	218-220
7d	B	CH_3OH—CH_3COCH_3	14	yellow needles	dec 260
7e	B	DMF	43	yellow powder	dec 353
7f	B	CH_3COCH_3	21	yellow needles	dec 295
7g	B	CH_3COCH_3	32	yellow powder	dec 350
7h	B	DMF	48	yellow powder	dec 350
9a	A	CH_3OH	72	yellow needles	269-270 dec (lit [1] 269-270 dec)
9b	A	CH_3OH	36	yellow needles	206-207
9g		CH_3COCH_3	10	yellow needles	271-274 dec
9h		C_6H_6	6	yellow needles	187-189 dec
10c	B	CH_3OH	7	yellow needles	dec 306
10d	B	CH_3OH	9	yellow powder	dec 272
10e	B	C_6H_6	4	yellow powder	310-312 dec
10f	B	DMF	10	yellow powder	dec 330
10g		CH_3COCH_3	14	orange needles	343-344 dec
10h		CH_3OH	10	yellow leaflets	216-218
12a	A	CH_3OH	58	yellow needles	275-277
12b	A	CH_3OH	22	yelow needles	dec 313
12c	B	CH_3COCH_3	19	yellow needles	dec 352

Table 2

Analytical and Spectral Data for Products **3**,**7**,**9**,**10**, and **12**.

Product No.	Molecular Formula	Analysis (%) Calcd./Found C	H	N	^{1}H-NMR (δ ppm) (DMSO-d_6)	IR (cm^{-1}) (potassium bromide)
3	$C_{11}H_4N_6$	60.00 60.34	1.83 1.78	38.17 38.04	7.5 (t, 8-H, 1H), 8.1 (m, 6-H, 7-H, 2H), 9.3 (d, 9-H, 1H)	2220, 1640, 1590, 1560, 1480, 1440, 1410, 1320, 1290, 1220, 1120, 780
7a	$C_{12}H_6N_6$	61.54 61.88	2.58 2.29	35.88 35.48	2.65 (s, CH_3, 3H), 7.38 (d, 8-H, 1H), 7.87 (s, 6-H, 1H), 9.2 (d, 9-H, 1H)	3040, 2220, 1640, 1580, 1500, 1450, 1420, 1320, 1280, 1230, 1160, 1140
7b	$C_{14}H_{10}N_6$	64.11 64.33	3.84 3.45	32.04 31.75	1.0 (t, CH_3, 3H), 1.8 (m, CH_2, 2H), 2.8 (t, CH_2, 2H), 7.39 (d, 8-H, 1H), 7.8 (s, 6-H, 1H), 9.17 (d, 9-H, 1H)	2920, 2220, 1640, 1580, 1490, 1450, 1310, 1220, 1130, 780
7c	$C_{15}H_{12}N_6$	65.21 65.36	4.38 4.10	30.42 30.63	1.4 (s, t-C_4H_9, 9H), 7.6 (d, 8-H, 1H), 7.85 (s, 6-H, 1H), 9.2 (d, 9-H, 1H)	2960, 2220, 1640, 1580, 1440, 1410, 1310, 1230, 1110, 790
7d	$C_{18}H_8N_6O$	66.67 66.81	2.47 2.37	25.93 25.99	7.6-8.0 (m, 8-H, Ph, 6H), 8.23 (s, 6-H, 1H), 9.4 (d, 9-H, 1H)	3050, 2220, 1640, 1570, 1480, 1440, 1280, 1230, 1100, 890, 710
7e	$C_{12}H_5N_7O$	54.76 54.83	1.91 1.86	37.25 37.35	7.73 (d, 8-H, 1H), 8.43 (s, 6-H, 1H), 9.33 (d, 9-H, 1H)	3380, 2800, 2220, 1680, 1620, 1500, 1460, 1400, 1230, 1120, 770
7e	$C_{12}H_5N_7O$	54.76 54.83	1.91 1.86	37.25 37.35	7.73 (d, 8-H, 1H), 8.43 (s, 6-H, 1H), 9.33 (d, 9-H, 1H)	3380, 2800, 2220, 1680, 1620, 1500, 1460, 1400, 1230, 1120, 770
7f	$C_{13}H_6N_6O_2$	56.12 56.16	2.17 1.97	30.21 30.41	4.0 (s, CH_3, 3H), 7.7 (d, 8-H, 1H), 8.46 (s, 6-H, 1H), 9.4 (d, 9-H, 1H)	3100, 2240, 1740, 1660, 1500, 1450, 1420, 1290, 1230, 1090, 760
7g	$C_{17}H_8N_6$	68.91 68.94	2.72 2.71	28.36 28.12	7.7 (m, Ph, 5H), 8.3 (d, 8-H, 1H), 8.5 (s, 6-H, 1H), 9.3 (d, 9-H, 1H)	3080, 2240, 1620, 1500, 1430, 1330, 1220, 1150, 760
7h	$C_{16}H_7N_7$	64.65 64.85	2.37 1.99	32.98 33.15	8.2-9.2 (m, 6-H, 8-H, 7-C_5H_4N, 6H), 9.6 (d, 9-H, 1H)	3050, 2240, 1630, 1580, 1490, 1430, 1410, 1290, 1220, 1140, 980, 770
9a	$C_{12}H_6N_6$	61.54 61.92	2.58 2.29	35.88 36.03	2.67 (s, CH_3, 3H), 7.4 (t, 8-H, 1H), 8.0 (d, 7-H, 1H), 9.1 (d, 9-H, 1H)	2220, 1630, 1550, 1480, 1430, 1400, 1290, 1230, 1210, 1140, 760
9b	$C_{13}H_8N_6$	62.90 62.99	3.25 2.91	33.85 33.66	1.4 (t, CH_3, 3H), 3.1 (q, CH_2, 2H), 7.4 (t, 8-H, 1H), 8.06 (d, 7-H, 1H), 9.07 (d, 9-H, 1H)	3000, 2220, 1630, 1550, 1480, 1430, 1410, 1290, 1210, 1140, 760
9g	$C_{17}H_8N_6$	68.91 69.25	2.72 2.63	28.36 28.63	7.5-8.4 (m, Ph, 7-H, 8-H, 7H), 9.3 (d, 9-H, 1H)	2240, 1630, 1580, 1480, 1440, 1410, 1320, 1290, 1170, 1150, 760
9h	$C_{15}H_{10}N_6O_2$	58.82 58.71	3.29 3.24	27.44 27.36	1.3 (t, CH_3, 3H), 4.1 (q, OCH_2, 2H), 4.2 (s, 6-CH_2, 2H), 7.47 (t, 8-H, 1H), 8.13 (d, 7-H, 1H), 9.2 (d, 9-H, 1H)	2980, 2230, 1730, 1630, 1550, 1480, 1430, 1290, 1180, 1130, 760
10c	$C_{12}H_5N_7O$	54.76 54.86	1.91 1.79	37.25 36.98	8.0 (d, 6-H, 1H), 8.47 (d, 7-H, 1H), 9.73 (s, 9-H, 1H)	3410, 2220, 1660, 1640, 1600, 1480, 1430, 1370, 1310, 1220, 760
10d	$C_{13}H_6N_6O_2$	56.12 56.39	2.17 2.18	30.21 30.07	4.0 (s, CH_3, 3H), 8.1 (d, 6-H, 1H), 8.3 (d, 7-H, 1H), 9.57 (s, 9-H, 1H)	3080, 2240, 1730, 1650, 1490, 1440, 1400, 1290, 1130, 760
10e	$C_{16}H_7N_7$	64.65 64.68	2.37 1.96	32.98 32.93	7.4-9.0 (m, 6-H, 7-H, 8-C_5H_4N, 6H), 9.9 (s, 9-H, 1H)	3050, 2220, 1630, 1580, 1460, 1420, 1310, 1290, 1230, 760

Table 2

(Continued)

Product No.	Molecular Formula	Analysis (%) Calcd./Found C	H	N	^{1}H-NMR (δ ppm) (DMSO-d_6)	IR (cm^{-1}) (potassium bromide)
10f	$C_{16}H_7N_7$	64.65 64.36	2.37 2.28	32.98 32.60	7.6 (t, 5′-H, 1H), 8.2 (d, 6-H, 1H), 8.4 (d, 6′-H, 1H), 8.6 (d, 7-H, 1H), 8.7 (d, 4′-H, 1H), 9.2 (s, 2′-H, 1H), 9.7 (s, 9-H, 1H)	3040, 2230, 1640, 1550, 1460, 1430, 1310, 1230, 1120, 790
10g	$C_{17}H_8N_6$	68.91 69.16	2.72 2.44	28.36 28.52	7.5 (m, Ph, 3H), 7.9 (m, Ph, 2H), 8.1 (d, 6-H, 1H), 8.5 (d, 7-H, 1H), 9.5 (s, 9-H, 1H)	3080, 2240, 1640, 1560, 1440, 1390, 1320, 1230, 1120, 820, 760
10h	$C_{15}H_{10}N_6O_2$	58.82 58.67	3.29 3.30	27.44 27.27	1.6 (t, CH_3, 3H), 3.97 (s, 8-CH_2, 2H), 4.13 (q, OCH_2, 2H), 8.0 (s, 6-H, 7-H, 2H), 9.2 (s, 9-H, 1H)	2970, 2230, 1720, 1640, 1560, 1480, 1310, 1230, 1200, 1140, 1010, 780
12a	$C_{13}H_8N_6$	62.90 63.18	3.25 3.19	33.85 33.46	2.5 (s, 8-CH_3, 3H), 2.68 (s, 6-CH_3, 3H), 7.93 (s, 7-H, 1H), 9.03 (s, 9-H, 1H)	2920, 2230, 1640, 1560, 1440, 1380, 1280, 1200, 1160, 970, 820, 750
12b	$C_{13}H_8N_6$	62.90 62.56	3.25 2.89	33.85 33.58	2.6 (s, 6-CH_3, 7-CH_3, 6H), 7.45 (d, 8-H, 1H), 9.1 (d, 9-H, 1H)	3100, 2220, 1640, 1560, 1500, 1440, 1420, 1340, 1270, 1170, 1140
12c	$C_{15}H_6N_6$	66.67 66.87	2.24 2.09	31.09 30.84	7.7 (d, 5-H, 1H), 7.95 (t, 2-H, 1H), 8.05 (t, 3-H, 1H), 8.15 (d, 1-H, 1H), 8.8 (d, 4-H, 1H), 8.9 (d, 6-H, 1H)	2240, 1640, 1570, 1500, 1460, 1400, 1360, 1320, 1210, 1130, 800

pyridine nucleus, such as 3-cyano- (**8i**), 3-formyl- (**8j**) and 3-acetyl (**8k**) groups, inhibited the reaction again. A theoretical explanation on the selectivity of the ring closing direction of 3-substituted pyridines with **2** is yet under investigation.

The reaction of **2** with other pyridines than mono-substituted ones was also carried out (Scheme 7). While 3,5-dimethylpyridine (**11a**) gave the expected 6,8-dimethyl derivative **12a**, unsymmetrical 3,4-dimethylpyridine (**11b**) reacted at its 1,2-position to afford the 6,7-dimethyl product **12b**. And isoquinoline (**11c**) cyclized at its 1,2-position to yield 9,10-dicyanopyrazino[2′,3′:4,5]imidazo[2,1-*a*]isoquinoline (**12c**), whereas quinoline (**11d**) did not react.

EXPERIMENTAL

Melting points were determined in a capillary and are uncorrected. The ir spectra were taken on a JASCO A-100 spectrometer in potassium bromide pellets. The ^{1}H-nmr spectra were recorded on a JEOL JNM-PMX 60 or a JEOL GX-270 spectrometer in DMSO-d_6 as a solvent. Chemical shifts are reported in δ ppm downfield from TMS as the internal standard. The starting material, 2,3-dichloro-5,6-dicyanopyrazine (**1**), was prepared from diaminomaleonitrile according to our previously reported procedure [1], and substituted pyridines were of commercial origin. Preparative and physical data of the obtained pyrido[1′,2′:1,2]imidazo[4,5-*b*]pyrazines are summarized in Table 1, and their analytical and spectral data in Table 2.

2-Amino-3-chloro-5,6-dicyanopyrazine (**2**).

Anhydrous ammonia gas was bubbled into a solution of **1** (2.0 g, 10 mmoles) in dimethylformamide (25 ml) under cooling at −10° for 15 minutes. Then the reaction mixture was evaporated to dryness *in vacuo*. The resulting residue was extracted with acetone and the acetone solution was evaporated again to give a solid, which was recrystallized from benzene to afford **2** (1.1 g, 61%) as pale yellow needles, mp 202-203°. In place of ammonia gas, ammonium carbonate (0.86 g, 9 mmoles) was also used successfully. After the solution was stirred at room temperature for 8 hours, a similar procedure was followed to give **2** (1.0 g, 56%); ir: 3420, 3320, 2230, 1610, 1540, 1510, 1400, 1140, 1050 cm^{-1}.

Anal. Calcd. for $C_6H_2ClN_5$: C, 40.13; H, 1.12; N, 39.00. Found: C, 40.42; H, 1.06; N, 38.96.

2,3-Dicyanopyrido[1′,2′:1,2]imidazo[4,5-*b*]pyrazines **3**, **7a-h**, **9a-b**, **10c-f**, and **12a-c**. General Procedure.

Method A.

The substrate **2** (0.30 g, 1.67 mmoles) was dissolved in pyridines (5 ml) and kept stirring at room temperature for 24 hours. The resulting precipitates were collected on a filter and recrystallized to give the corresponding products **3**, **7a**, **9a-b**, and **12a-b**.

Method B.

A solution of **2** (0.30 g, 1.67 mmoles) and pyridines (5.0 mmoles) in dimethylformamide (7 ml) was heated at about 90° for 48 hours. The resulting precipitates were collected on a filter and recrystallized to afford the corresponding products **7h**, **10f**, and **12c**. In case that no precipitate appeared, the mixture was evaporated to dryness under reduced pressure to leave a solid, which was washed with the least amount of cold methanol or acetone and then recrystallized to yield the products **7b-g**, and **10c-e**.

2,3-Dicyano-6- and 8-phenylpyrido[1′,2′:1,2]imidazo[4,5-*b*]pyrazines (**9g**, **10g**).

A solution of **2** (0.30 g, 1.67 mmoles) and **8g** (0.78 g, 5.0 mmoles) in dimethylformamide (7 ml) was heated at 90° for 48 hours. The precipitates were collected on a filter and recrystallized from acetone to give the 8-phenyl product **10g** (0.07 g, 14%). The filtrate was combined with the acetone mother liquor and evaporated to dryness *in vacuo*, and then the resulting solid was recrystallized from acetone to give the 6-phenyl isomer **9g** (0.05 g, 10%).

2,3-Dicyano-6- and 8-ethoxycarbonylmethylpyrido[1',2':1,2]imidazo-[4,5-*b*]pyrazines (**9h**, **10h**).

A solution of **2** (0.30 g, 1.67 mmoles) and **8h** (0.83 g, 5.0 mmoles) in dimethylformamide (7 ml) was heated at 90° for 48 hours. After removal of the solvent *in vacuo*, the residual solid was washed with least amount of cold methanol and recrystallized from methanol to afford the 8-ethoxycarbonylmethyl product **10h** (0.05 g, 10%). The methanol mother liquor was evaporated to give a solid, which was recrystallized from benzene to yield the 6-ethoxycarbonylmethyl isomer **9h** (0.03 g, 6%).

REFERENCES AND NOTES

[1] T. Suzuki, Y. Nagae and K. Mitsuhashi, *J. Heterocyclic Chem.*, **23**, 1419 (1986).