Synthesis of Pyrido[1′,2′:1,2]imidazo[4,5-*b*]pyrazines from 2,3-Dichloro-5,6-dicyanopyrazine with 2-Aminopyridines

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Novel synthesis of the title compounds by the facile cyclization between 2,3-dichloro-5,6-dicyanopyrazine and various 2-aminopyridines under relatively mild conditions is described. The reactivity depended on the basicity of 2-aminopyridines.

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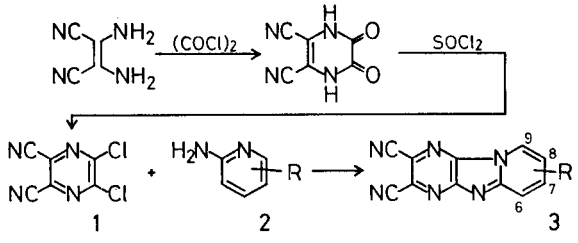
Oligofused heterocyclic compounds bearing a bridgehead nitrogen atom are expected to be of pharmacological interest [1]. However, the preparation of pyrido[1′, 2′:1, 2]imidazo[4,5-*b*]pyrazines has been little explored and only a complicated route from 2-aminopyrazine-4-oxide with refluxing pyridine has been reported [2].

Previously, as a part of studies on pyrazine chemistry, we reported [3] the synthesis of fused pyrazines such as pyrazino[2,3-*b*]pyrazines by the cyclization of various *vic*-bifunctional nucleophiles with 2,3-dichloro-5,6-dicyanopyrazine (**1**), which was prepared in a high yield from diaminomaleonitrile as a starting material. We extended our studies on the pyrazine chemistry and report, in the present paper, the preparation of 2,3-dicyanopyrido-[1′, 2′:1,2]imidazo[4,5-*b*]pyrazines **3**, bearing a bridgehead nitrogen atom at 10-positon, in appreciable yields by the facile cyclization between **1** and 2-aminopyridines **2** under such mild conditions as in dioxane at room temperature or, at most, 80°.

Recrystallization solvent, appearance, melting point and yield of the products **3** are summarized in Table 1,

Scheme



R	R
2a: H	3a: H
2b: 3-CH_3	3b: 6-CH_3
2c: 4-CH_3	3c: 7-CH_3
2d: 5-CH_3	3d: 8-CH_3
2e: 6-CH_3	3e: 9-CH_3
2f: 4,6-$(CH_3)_2$	3f: 7,9-$(CH_3)_2$
2g: 3-$OCH_2C_6H_5$	3g: 6-$OCH_2C_6H_5$
2h: 5-Cl	3h: 8-Cl
2i: 5-Br	3i: 8-Br

Table 1

Basicity of **2**, Reaction Temperature and Physical Properties for Products **3**

	2-Aminopyridines **2**			2,3-Dicyanopyrido[1′,2′:1,2]imidazo[4,5-*b*]pyrazines **3**				
Suffix of **2** & **3**	Substituent R	p*Ka*	Reaction Temperature [a]	Substituent R	Recrystallization Solvent	Appearance	Mp (°C)	Yield (%)
a	H	6.82	room	H	CH_3OH	yellow needles	317-319 dec	79
b	3-CH_3	6.88	room	6-CH_3	CH_3OH	yellow leaflets	269-270 dec	80
c	4-CH_3	7.29	room	7-CH_3	CH_3OH	yellow needles	286-288	91
d	5-CH_3	7.02	room	8-CH_3	CH_3OH	yellow powder	dec. 309	63
e	6-CH_3	7.24	room	9-CH_3	CH_3OH	yellow needles	dec. 280	79
f	4,6-$(CH_3)_2$	7.72	room	7,9-$(CH_3)_2$	CH_3OH	yellow needles	238-240	48
g	3-$OCH_2C_6H_5$	6.39	room	6-$OCH_2C_6H_5$	CH_3COCH_3-$CHCl_3$	yellow needles	263-264 dec	54
h	5-Cl	4.90	80°	8-Cl	CH_3OH	yellow powder	dec. 265	47
i	5-Br	5.01	80°	8-Br	CH_3OH	yellow needles	341-343	15
j	3,5-Cl_2	3.08	reflux	6,8-Cl_2	–	–	–	none
k	3,5-Br_2	2.73	reflux	6,8-Br_2	–	–	–	none
l	3-NO_2	2.73	reflux	6-NO_2	–	–	–	none
m	5-NO_2	2.88	reflux	8-NO_2	–	–	–	none

[a] Dioxane was used as a reaction solvent in all runs.

Table 2

Analytical and Spectral Data for Products **3**

Compound No.	Molecular Formula	Analyses (%) Calcd./Found C	H	N	^{1}H-NMR (δ ppm) (DMSO-d_6)	IR (ν cm^{-1}) (KBr)
3a	$C_{11}H_4N_6$	60.00	1.83	38.17	7.5 (t, 8-H, 1H), 8.1 (m, 6-H, 7-H, 2H),	2220, 1640, 1480, 1440,
		60.20	1.64	38.20	9.3 (d, 9-H, 1H)	1410, 1320, 1290, 1220, 1120
3b	$C_{12}H_6N_6$	61.54	2.58	35.88	2.7 (s, 6-CH_3, 3H), 7.4 (t, 8-H, 1H),	2220, 1630, 1550, 1480,
		61.76	2.40	36.09	8.0 (d, 7-H, 1H), 9.1 (d, 9-H, 1H)	1430, 1400, 1290, 1230, 1210, 1140
3c	$C_{12}H_6N_6$	61.54	2.58	35.88	2.6 (s, 7-CH_3, 3H), 7.3 (d, 8-H, 1H),	2220, 1640, 1580, 1500,
		61.68	2.29	35.45	7.9 (s, 6-H, 1H), 9.2 (d, 9-H, 1H)	1450, 1420, 1320, 1280, 1230. 1210. 1160. 1140
3d	$C_{12}H_6N_6$	61.54	2.58	35.88	3.3 (s, 8-CH_3, 3H), 8.1 (s, 6-H, 7-H, 2H),	2240, 1650, 1580, 1450,
		61.95	2.52	35.47	9.2 (s, 9-H, 1H)	1390, 1320, 1230, 1105, 1000, 820
3e	$C_{12}H_6N_6$	61.54	2.58	35.88	3.15 (s, 9-CH_3, 3H), 7.4 (d, 8-H, 1H),	2220, 1640, 1560, 1490,
		61.82	2.16	36.02	8.0 (s, 6-H, 7-H, 2H)	1430, 1310, 1230, 1110, 790
3f	$C_{13}H_8N_6$	62.90	3.25	33.85	2.55 (s, 7-CH_3, 3H), 3.05 (s, 9-CH_3, 3H),	2240, 1660, 1570, 1500,
		63.19	3.16	33.59	7.15 (s, 6-H, 1H), 7.65 (s, 8-H, 1H)	1440, 1400, 1330, 1280, 1220, 1170, 850
3g	$C_{18}H_{10}N_6O$	66.28	3.07	25.75	5.5 (s, 6-OCH_2,2H), 7.5 (m, 7-H, 8-H, 6-Ph, 7H),	2240, 1640, 1550, 1480,
		66.49	2.74	25.36	8.9 (d, 9-H, 1H)	1440, 1290, 1130, 1010, 740
3h	$C_{11}H_3N_6Cl$	51.89	1.19	33.00	8.15 (s, 6-H, 7-H, 2H), 9.65 (s, 9-H, 1H)	2250, 1640, 1565, 1470,
		51.91	1.10	32.91		1310, 1230, 1080, 830, 735
3i	$C_{11}H_3N_6Br$	44.17	1.01	28.10	8.2 (s, 6-H, 7-H, 2H), 9.7 (s, 9-H, 1H)	2240, 1630, 1540, 1460,
		44.51	0.79	28.22		1300, 1230, 1140, 810

together with basic pK_a value of **2** and reaction conditions. Structures of **3** were elucidated by elemental analyses, ^{1}H-nmr and ir spectroscopy, and those data are shown in Table 2.

While 2-aminopyridines **2a-g** of higher pK_a reacted readily at room temperature, higher reaction temperature up to 80° was needed in the cases with **2h** and **2i** because of lower pK_a. And much weaker bases such as 3, 5-dichloro- **(2j)**, 3,5-dibromo- **(2k)**, 3-nitro- **(21)** and 5-nitro-2-aminopyridine **(2m)** did not react, recovering the substrates, even under refluxing temperature of the solvent and no expected signal of the product could be observed with hplc. Consequently it can be said that the basicity of 2-aminopyridines affects the reactivity and the strong electron withdrawing group prohibits the reaction.

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 disks. The ^{1}H-nmr spectra were recorded on a JEOL JNM-PMX 60 or a JEOL GX-270 spectrometer in DMSO-d_6. Chemical shifts in Table 2 are reported in δ ppm downfield from TMS as the internal standard. 2-Aminopyridines **2** were commercially obtained. The pK_a values of conjugate acids of **2** were measured at 25° by means of the conventional potentiometric titration and the reliability was approved by comparison of the observed value (pK_a = 6.82) of 2-aminopyridine **(2a)** with that in literature (pK_a = 6.86) [4].

2,3-Dichloro-5,6-dicyanopyrazine **(1)**.

The substrate **1** was prepared from diaminomaleonitrile as reported previously [3]. Namely, to a solution of oxalyl chloride (25 g, 0.2 mole) in dry dioxane (50 ml), a suspension of diaminomaleonitrile (21.6 g, 0.2 mole) in dioxane (100 ml) was added dropwise under cooling in an ice-water bath. After the exotherm ceased, the mixture was stirred at room temperature for 1 hour and successively at 50° for 4 hours, and then kept standing at room temperature. The resulting precipitates were collected on a filter, washed with hexane and recrystallized from water, giving white needles (29.1 g, 90%) of 5,6-dicyano-2,3-dioxo-1,2,3,4-tetrahydropyrazine, mp 268-270° (lit [3,5] 270°).

To a suspension of thus obtained dioxopyrazine (20 g, 0.12 mole) in dioxane (150 ml) were added dimethylformamide (1 ml) and thionyl chloride (27 ml, 0.36 mole). The mixture was heated at 100° for 5 hours with stirring and then evaporated to dryness under reduced pressure to leave a solid, which was extracted with hot toluene. Removal of the solvent under reduced pressure gave a residual solid, which was recrystallized from chloroform to afford white needles **1** (22 g, 90%), mp 179-180° (lit [3] 180°).

Anal. Calcd. for $C_6N_4Cl_2$: C, 36.21; N, 28.15. Found: C, 36.03; N, 28.45.

2,3-Dicyanopyrido[1′, 2′: 1,2]imidazo[4,5-*b*]pyrazine **(3a)**.

A solution of **1** (1.00 g, 5 mmoles) and **2a** (1.13 g, 12 mmoles) in dioxane (50 ml) was stirred at room temperature for 24 hours. After removal of the solvent under reduced pressure, the resulting yellow solid was washed with least amount of cold methanol and then recrystallized from methanol to yield **3a** (0.87 g, 79%) as yellow needles.

Other pyridoimidazopyrazines **3b-3i** were prepared by similar procedures, except the reaction temperature at 80° in cases of **3h** and **3i**.

REFERENCES AND NOTES

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