Facile Preparation of 6-Bromopyridine-2-carboxamide and Pyridine-2,6-dicarboxamide: Partial Aminocarbonylation of 2,6-Dibromopyridine

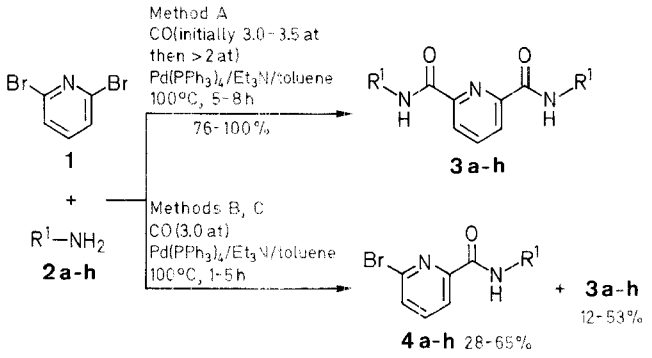
Hiroshi Horino,* Hiroyuki Sakaba, Mannosuke Arai

Department of Chemistry, College of General Education, Tohoku University, Kawauchi, Sendai 980, Japan

The palladium-catalyzed carbonylation of 2,6-dibromopyridine in the presence of primary amines under controlled conditions (carbon monoxide pressure) gives mainly *N*-aryl- or *N*-alkyl-6-bromopyridine-2-carboxamides accompanied by *N,N'*-diaryl- or *N,N'*-dialkylpyridine-2,6-dicarboxamides. Further aminocarbonylation of the *N*-aryl- and *N*-alkyl-6-bromopyridine-2-carboxamides affords unsymmetric *N,N'*-diaryl, *N*-alkyl-*N'*-aryl-, or *N,N'*-dialkylpyridine-2,6-dicarboxamides.

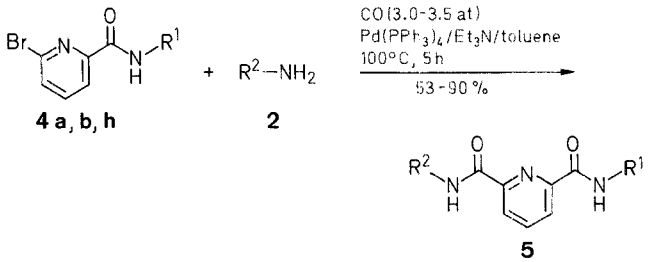
Pyridines having acyclic or cyclic O- or N-containing substituents in the 2- and 6-positions are utilized as polydentate ligands.[1] Some 6-substituted pyridine-2-carboxamides have been used as models of the anti-tumor agent Bleomycin.[2] *N,N'*-Disubstituted pyridine-2,6-dicarboxamides are usually prepared from pyridine-2,6-dicarboxylic acid by acid chloride formation followed by amidation;[3] however, this method is limited to symmetrical diamides. Reported advances in the palladium-catalyzed carbonylation producing *N*-arylcarboxamides[4] and heterocyclic compounds[5] made us study the aminocarbonylation of easily available 2,6-dihalopyridines. There are already several reports on the twofold carbonylation of organic halides.[6] However, little attention has hitherto been paid to the selectivity in the palladium-catalyzed partial carbonylation of organic dihalides and to its application to organic syntheses. We now present an example of the selective mono-aminocarbonylation of 2,6-dibromopyridine (**1**), which affords the potentially useful synthetic intermediates *N*-aryl- or *N*-alkyl-6-bromopyridine-2-carboxamides **4** as well as the corresponding *N,N'*-disubstituted pyridine-2,6-dicarboxyamides **3**. These reactions were carried out by heating toluene solutions of **1** and primary aromatic or aliphatic amines **2a–h** in the presence of triethylamine and catalytic amounts of

tetrakis(triphenylphosphine)palladium(0) under an initial pressure of 3–3.5 at of carbon monoxide. Maintaining more than 3 at carbon monoxide pressure over the reaction time (Method A) leads to precipitation of *N,N'*-diaryl- or *N,N'*-dialkylpyridine-2,6-dicarboxamides **3a–h**, most of which are readily isolated by filtration of the reaction mixture. Reduction of carbon monoxide pressure and/or reaction time (Method B) affords the monocarbonylation products, *N*-aryl- or *N*-alkyl-6-bromopyridine-2-carboxamides **4a–h** as the main products, at the expense of **3a–h**.



Use of equimolecular amounts of amines **2** gives rise to a different mono-aminocarbonylation (Method C); this is especially useful with aliphatic amines **2f–h** because there is a distinct difference in reaction rates between aromatic amines (e.g., **2a**) and aliphatic amines (e.g. **2h**) as observed by monitoring the carbon monoxide pressure. To complete the reaction according to Method C, **2a** requires 1 day, whereas **2h** requires only 3 h. In the attempted reaction with a secondary amine, namely *N*-methylaniline, compound **1** remained unchanged and was recovered under the conditions of Method A.

Further carbonylation of *N*-phenyl- or *N*-(4-methylphenyl)-6-bromopyridine-2-carboxamide (**4a** or **4b**, respectively) with amines **2b–d, g–i** under similar conditions gave unsymmetric *N,N'*-diaryl- or *N*-alkyl-*N'*-arylpyridine-2,6-dicarboxamides **5**. Similarly, the reaction of **4h** with **2g** and **2i** afforded the corresponding diamides **5hg** and **5gi**, respectively.



This stepwise carbonylation provides a new method for preparing 2,6-difunctionalized pyridines, for example, unsymmetric *N,N'*-disubstituted pyridine-2,6-dicarboxamides which are not easily accessible other routes. It is worthy of note that carbon monoxide pressures of relatively limited ranges control the formation of mono- and bis-aminocarbonylation products from 2,6-dibromopyridine (**1**).

Commercially available reagents were used without purification. Toluene was distilled from Na and stored under N_2 before use. $Pd(PPh_3)_4$ was prepared according to the literature.[9] Column chromatography was performed using Wako C-300 (300 mesh) silica gel. Microanalyses were performed by Instrumental Analysis Center, Faculty of Science, Tohoku University.

Table 1. Preparation of Pyridine-2,6-dicarboxamides **3** and 6-Bromopyridine-2-carboxamides **4**

Amine	R^1	Method	Conversion (%)	Diamide	Yield[a] (%)	Monoamide	Yield[b] (%)
2a	Ph	A		**3a**	90		
		B	84	**3a**	37[b]	**4a**	55
2b	4-MeC_6H_4	A		**3b**	76		
		B	66	**3b**	16[b]	**4b**	36
2c	4-$MeOC_6H_4$	A		**3c**	78		
		B	68	**3c**	26[b]	**4c**	28
2d	4-ClC_6H_4	A		**3d**	**100**		
		B		**3d**	53	**4d**	25[a]
2e	2-pyridyl	A		**3e**	95		
		B	72	**3e**	35[b]	**4e**	47
2f	$PhCH_2$	A		**3f**	76		
		B	88	**3f**	12[b]	**4f**	49
2g	*c*-C_6H_{11}	A		**3g**	90		
		B	79	**3g**	19[b]	**4g**	65
2h	*n*-C_6H_{13}	A		**3h**	93		
		B	85	**3h**	32[b]	**4h**	55
		C	77	**3h**	30[b]	**4h**	57

[a] Yield of isolated product based on **1**

[b] Yield based on **1** using the percentage conversion indicated in this table.

Table 2. Preparation of Unsymmetric Pyridine-2,6-dicarboxamides **5**

Monoamide	R^1	Amine	R^2	Diamide	Yield[a] (%)
4a	Ph	**2b**	4-MeC_6H_4	**5ab**	70
4b	4-MeC_6H_4	**2c**	4-$MeOC_6H_4$	**5bc**	59
4b	4-MeC_6H_4	**2d**	4-ClC_6H_4	**5bd**	53
4a	Ph	**2g**	*c*-C_6H_{11}	**5ag**	85
4a	Ph	**2h**	*n*-C_6H_{13}	**5ah**	87
4a	C_6H_5	**2i**	*t*-C_4H_9	**5af**	76
4h	*n*-C_6H_{13}	**2g**	*c*-C_6H_{11}	**5hg**	90
4h	*n*-C_6H_{13}	**2i**	*t*-C_4H_9	**5hi**	85

[a] Yield of isolated product based on monoamide **4**.

***N,N'*-Diaryl- or *N,N'*-Dialkylpyridine-2,6-dicarboxamides 3a–h and *N*-Aryl- or *N*-Alkyl-6-bromopyridine-2-carboxamides 4a–h; General Procedure:**

Method A: A mixture of 2,6-dibromopyridine (**1**; 1.19 g, 5.0 mmol), the aromatic amine **2a–e** or aliphatic amine **2f–h** (11.0 mmol), and $Pd(PPh_3)_4$ (0.30 g, 0.26 mmol) is placed in a thick-wall glass vessel (50 mL) under N_2, and toluene (10 mL) and Et_3N (2 mL) are added successively. The vessel is placed in an autoclave (Taiatsu Glass Industry Co., Ltd.), and N_2 is replaced by CO (3.5 at). The mixture is stirred at 100°C for 5–8 h. Additional CO is introduced 2 or 3 times to maintain the pressure above 3.0 at. The mixture is then cooled to room temperature and the precipitate is isolated by suction and washed with toluene and with H_2O to give the crude product **3a–g**, which is purified by recrystallization from the solvents specified in Table 3. Product **3h** is isolated by column chromatography on silica gel using EtOAc/benzene (1:4) as eluent.

Method B: A solution of 2,6-dibromopyridine (**1**; 1.19 g, 5.0 mmol), the aromatic amine **2a–e** or aliphatic amine **2f–h** (11.0 mmol), and $Pd(PPh_3)_4$ (0.30 g, 0.26 mmol) in toluene (10 mL)/Et_3N (2 mL) is placed in a reaction vessel and CO (3 at) is introduced. The mixture is heated at 100°C for 3–5 h (**3–f**) or 1 h (**3g, h**), then cooled to room temperature. The precipitate is isolated by suction to give product **3a–g**. The filtrate is shaken with 2 M HCl (2 × 10 mL), washed with H_2O (3 × 10 mL), and dried (Na_2SO_4). The solvent is removed under reduced pressure and the residue is column-chromatographed on silica

Table 3. Properties of Pyridine-2,6-dicarboxamides **3,5** and 6-Bromopyridine-2-carboxamides **4**

Product	mp (°C)[a] (solvent)	Molecular Formula[b] or mp (°C) reported	IR,[c] ν (cm^{-1})	^{1}H-NMR (solvent/TMS)[d] δ, J (Hz)
3a	278 (acetone)	285[7]	3275, 1675, 1660, 1595, 1550	7.07–7.42 (m, 6H); 7.90 (d, 4H, J = 8); 8.31 (m, 3H); 11.02 (s, 2H)
3b	224 (THF/EtOH)	$C_{21}H_{19}N_3O_2$ (345.4)	3240, 1675, 1660, 1590, 1550	2.27 (s, 6H); 7.08 (d, 4H, J = 9); 7.55 (d, 4H, J = 9); 8.01 (AB_2, 1H, J = 8); 8.37 (AB_2, 2H, J = 8); 9.46 (s, 2H)
3c	281 (DMF)	$C_{21}H_{19}N_3O_4$ (377.4)	3280, 1670, 1650, 1590, 1555	3.72 (s, 6H); 6.86 (d, 4H, J = 8); 7.61 (d, 4H, J = 8); 8.15 (m, 3H); 10.50 (s, 2H)
3d	248 (THF)	$C_{19}H_{13}Cl_2N_3O_2$ (386.2)	3300, 1685, 1665, 1590, 1550	7.35 (d, 4H, J = 9); 7.71 (d, 4H, J = 9); 8.14 (AB_2, 1H, J = 8); 8.48 (AB_2, 2H, J = 8); 9.43 (s, 2H)
3e	232 (THF)	225–226[8]	3300, 1702, 1582, 1550	7.21 (dd, 3H, J = 6, 9); 7.87 (dt, 3H, J = 2, 9); 8.22–8.32 (m, 5H); 9.53 (s, 2H)
3f	185 (THF/EtOH)	179–181[8]	3300, 1675, 1655, 1545	4.62 (d, 4H, J = 7); 7.32 (s, 10H); 8.24 (t, 3H); 9.86 (t, 2H)
3g	235 ($CHCl_3$/benzene)	$C_{19}H_{27}N_3O_2$ (329.4)	3295, 1665, 1650, 1545	1.10–2.25 (m, 20H); 3.80–4.20 (m, 2H); 7.61 (br d, 2H, J = 8); 8.00 (AB_2, 1H, J = 8); 8.34 (AB_2, 2H, J = 8)
3h	oil	$C_{19}H_{31}N_3O_2$ (333.5)	3330, 1680, 1660, 1540	0.70–2.00 (m, 22H); 3.50 (q, 4H, J = 6); 7.74 (br t, 2H, J = 6); 8.01 (AB_2, 1H, J = 8); 8.35 (AB_2, 2H, J = 8)
4a	114 (benzene)	$C_{12}H_9BrN_2O$ (277.1)	3330, 1680, 1600, 1530	7.10–7.45 (m, 4H); 7.60–7.80 (m, 3H); 8.21 (dd, 1H, J = 6, 2); 9.60 (s, 1H)
4b	105 (EtOH)	$C_{13}H_{11}BrN_2O$ (291.1)	3355, 1685, 1530	2.35 (s, 3H); 7.16 (d, 2H, J = 9); 7.64 (m, 4H); 8.32 (dd, 1H, J = 7, 2); 9.65 (s, 1H)
4c	90 (EtOH)	$C_{13}H_{11}BrN_2O_2$ (307.1)	3360, 1685, 1590, 1540, 1255	3.82 (s, 3H); 6.93 (d, 2H, J = 8); 7.67 (m, 4H); 8.26 (dd, 1H, J = 7, 2); 9.53 (s, 1H)
4d	122 (EtOH)	$C_{12}H_8BrClN_2O$ (311.6)	3270, 1685, 1600, 1590, 1530	7.33 (dd, 2H, J = 2, 8); 7.64–7.86 (m, 4H); 8.23 (dd, 1H, J = 2, 8); 9.45 (s, 1H)
4e	148 (EtOH)	$C_{11}H_8BrN_3O$ (278.1)	3385, 1705, 1580, 1530	7.05 (dd, 1H, J = 6, 8); 7.56–7.80 (m, 3H); 8.20 (dd, 1H, J = 2, 8); 8.33 (d, 2H, J = 6); 9.63 (s, 1H)
4f	116 (benzene/hexane)	$C_{13}H_{11}BrN_2O$ (291.1)	3330, 2940, 1670, 1560	4.55 (d, 2H, J = 8); 7.23 (s, 5H); 7.35 (dd, 2H, J = 8); 8.05 (d, 1H, J = 8); 8.08 (d, 1H, J = 8)
4g	oil	$C_{12}H_{15}BrN_2O$ (283.2)	3410, 1680, 1555, 1525	1.10–2.15 (m, 10H); 3.70–4.15 (m, 1H); 7.45–7.85 (m, 3H); 8.16 (dd, 1H, J = 7, 2)
4h	oil	$C_{12}H_{17}BrN_2O$ (285.2)	3420, 1685, 1555, 1530	0.75–1.90 (m, 11H); 3.45 (q, 2H, J = 7); 7.50–7.95 (m, 3H); 8.16 (dd, 1H, J = 7, 2)
5ab	219 (EtOH)	$C_{20}H_{17}N_3O_2$ (331.4)	3280, 1680, 1660, 1595, 1550	2.32 (s, 3H); 7.05–7.73 (m, 9H); 8.00 (dd, 1H, J = 7, 9); 8.40 (d, 2H, J = 8) 9.43 (s, 1H); 9.48 (s, 1H)
5bc	235 (THF)	$C_{21}H_{19}N_3O_3$ (361.4)	3280, 1675, 1655, 1550, 1510	3.30 (s, 3H); 3.79 (s, 3H); 7.01 (d, 2H, J = 8); 7.24 (d, 2H, J = 8); 7.96 (m, 4H, J = 8); 8.30 (m, 3H); 11.0 (s, 2H)
5bd	205 (THF/EtOH)	$C_{20}H_{16}ClN_3O_2$ (365.8)	3280, 1675, 1660, 1595, 1550	2.30 (s, 3H); 7.05 (d, 2H, J = 8); 7.24 (d, 3H, J = 7); 7.52 (d, 2H, J = 9); 7.65 (d, 2H, J = 9); 8.35 (d, 2H, J = 8); 9.40 (s, 1H); 9.54 (s, 1H)
5ag	237 (benzene/hexane)	$C_{19}H_{21}N_3O_2$ (323.4)	3275, 1675, 1645, 1550	1.05–2.30 (m, 10H); 3.80–4.30 (m, 1H); 7.05–7.85 (m, 6H); 7.95–8.50 (m, 3H); 9.49 (s, 1H)
5ah	97 (hexane)	$C_{19}H_{23}N_3O_2$ (325.4)	3295, 1680, 1650, 1550	0.75–1.90 (m, 11H); 3.53 (q, 2H, J = 7); 7.05–7.85 (m, 6H); 7.90–8.50 (m, 3H); 9.52 (s, 1H)
5af	193 (benzene/hexane)	$C_{17}H_{19}N_3O_2$ (297.4)	3310, 1680, 1660, 1535	1.56 (s, 9H); 7.05–7.85 (m, 6H); 7.95–8.50 (m, 3H); 9.48 (s, 1H)
5hg	129 (benzene/hexane)	$C_{19}H_{29}N_3O_2$ (331.5)	3330, 3295, 1685, 1645, 1535	0.75–2.20 (m, 21H); 3.50 (q, 2H, J = 7); 3.75–4.25 (m, 1H); 7.30–7.85 (m, 2H); 8.00 (AB_2, 1H, J = 8); 8.34 (AB_2, 2H, J = 8)
5hi	oil	$C_{17}H_{27}N_3O_2$ (305.4)	3335, 1680, 1660, 1530	0.80–1.90 (m, 20H); 3.51 (q, 2H, J = 6); 7.40–7.80 (m, 2H); 8.00 (AB_2, 1H, J = 8); 8.33 (AB_2, 2H, J = 8)

[a] Uncorrected, measured with Yanagimoto micromelting point apparatus.

[b] Satisfactory microanalyses: C ± 0.29, H ± 0.26, N ± 0.25; except **4b** (N − 0.44) and **4h** (C + 0.53).

[c] Recorded on a Hitachi 215 grating spectrophotometer. Neat for **3h**, **4g**, **4h**, **5hi**, and KBr for the other compounds.

[d] Recorded on a Hitachi R-90H FT-NMR spectrometer. DMSO-d_6 for **3a**, **3c**, **3e**, **3f**, **5bc**, and $CDCl_3$ for the other compounds.

gel (20.0 g) using benzene as eluent to yield **4a–g**. Products **3h** and **4h** are separated by column chromatography using EtOAc/benzene (1:8–1:4) as eluent.

Method C; Typical procedure: A solution of 2,6-dibromopyridine (**1**, 1.19 g, 5.0 mmol), 1-aminohexane (**2h**; 0.51 g, 5.0 mmol), Et_3N (2 mL), and $Pd(PPh_3)_4$ (0.30 g, 0.26 mmol) in toluene (10 mL) is heated at 100 °C for 5 h under a CO pressure of 3.0 at. The mixture is then cooled to room temperature and filtered. The filtrate is concentrated under reduced pressure and column-chromatographed on silica gel (50.0 g) using EtOAc/benzene (0:1–1:1) as eluent to afford products **3h** and **4h**; conversion: 77%; yield of **3h**: 0.38 g (30%, based on reacted **1**); yield of **4h**: 0.63 g (57%).

Unsymmetrical *N,N*'-Diaryl-, *N*-Alkyl-*N*'-aryl- and *N,N*'-Dialkylpyridine-2,6-dicarboxamides 5; General Procedure:

Carbon monoxide (3.5 at) is introduced into a toluene solution (5 mL) of **4a, b, h** (1.0 mmol), amine **2b–d, g–i** (1.1 mmol for **2b–d, g, h**; 10 mmol for **2i**), $Pd(PPh_3)_4$ (0.108 g, 0.08 mmol), and Et_3N (0.5 mL). The mixture is heated at 100 °C for 5 h (24 h for **2i**), then worked up and the product isolated as in Method A (**5ab, 5bc, 5bd, 5ag**), by chromatographed on silica gel followed by recrystallization (**5ah, 5af, 5hg**), or by Kugelrohr distillation (**5hi**).

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