Synthesis of Some 3,6-Disubstituted Pyridazines

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Some novel 3-halo-6-(4-substituted-phenoxy)pyridazines and 3,6-di-(4-substituted-phenoxy)pyridazines were synthesized from 3,6-dichloropyridazine or 3,6-diiodopyridazine. 3,6-Diiodopyridazine was prepared from 3,6-dichloropyridazine using hydriodic acid/iodine monochloride.

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Much attention has been focused on the synthesis of 3,6-disubstituted-pyridazine derivatives because they have exhibited various properties such as agrochemical activities [1-4], pharmacological activities [5-7], a catalyst for the dihydroxylation of olefins [8] and the metal chelating activities [9-15].

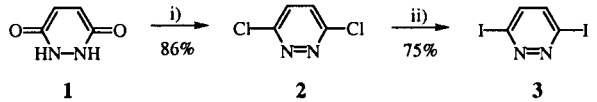
In connection with our research program for the study on the reactivity and the synthesis of novel 3,6-disubstituted-pyridazines, we required some 3,6-diphenoxy- or 3-alkoxy-6-substituted-pyridazines.

In this paper, we would like to report the synthesis of novel 3,6-diphenoxy- or 3-methoxy-6-substituted-pyridazines from 3,6-dichloropyridazine (**2**) or 3,6-diiodopyridazine (**3**).

3,6-Dichloropyridazine (**2**) was prepared from pyridazine-3,6-dione (**1**) by the reported method [16]. On the other hand, we attempted at first to prepare 3,6-diiodopyridazine (**3**) from **2** by Willkins's method [17]. The melting point of **3** prepared by Willkins's method is similar to the reported melting point [17]. However, the proton magnetic resonance spectrum of this compound showed two signals for aromatic protons at δ 7.46 ppm (s, 2H) for **2** and at δ 7.42 ppm (s, 2H) for **3**. Therefore, we attempted to synthesize pure compound **3** in good yield.

Iodination of **2** with hydriodic acid (55%)/iodine monochloride for 24 hours at 70° gave **3** in 75% yield (Scheme I). The proton resonance spectrum of **3** prepared by our method revealed only one proton signal as singlet for two aromatic protons at δ 7.42 ppm.

Scheme I



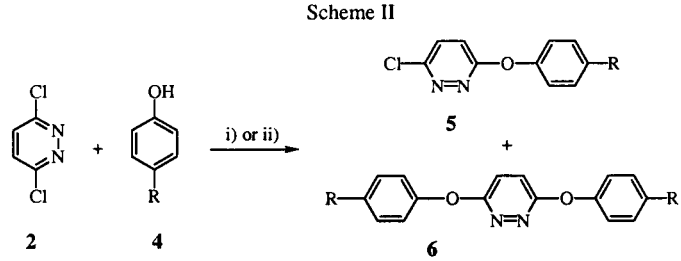
1 **2** **3**

i) $POCl_3$, reflux. ii) HI (55%)/ICl, 70°C.

Reaction of **2** with one equivalent of **4a** or **4c-4e** in the presence of potassium carbonate (1 equivalent) gave only 3-chloro-6-phenoxypyridazines **5a** or **5c-5e** (Scheme II). Whereas, treatment of **2** with one equivalent of *p*-chlorophenol (**4b**) in the presence of potassium carbonate (1 equivalent) yielded **5b** in 88% yield and **6b** in 2% yield.

Esterification of **2** with two equivalents of **4a-4c** in the presence of potassium carbonate (2 equivalents) also gave the corresponding 3,6-diphenoxypyridazines **6a-6c**. Whereas, compound **2** was reacted with two equivalents of **4d** or **4e** in the presence of potassium carbonate (2 equivalents) at reflux temperature for 0.2 hours (for **4d**) or 1.2 hours (for **4e**) to yield only **5d** (79%) or **5e** (69%) instead of the corresponding 3,6-diphenoxy derivatives. When the reaction time was longer than the optimum reaction time, we detected the formation of several products by tlc. These results may be due to the electron-withdrawing groups on the phenyl ring.

Scheme II



2 **4** **5** **6**

i) Method A; Phenol (1 equivalent), K_2CO_3 (1 equivalent), CH_3CN (or dimethylformamide).
ii) Method B; Phenol (2 equivalents), K_2CO_3 (2 equivalents), CH_3CN (or dimethylformamide).

R	OMe		Cl		NH_2		CN		NO_2	
	5a	**6a**	**5b**	**6b**	**5c**	**6c**	**5d**	**6d**	**5e**	**6e**
Method A	80	—	88	2	95	—	62	—	61	—
Method B	—	70	—	83	—	87	79	—	69	—

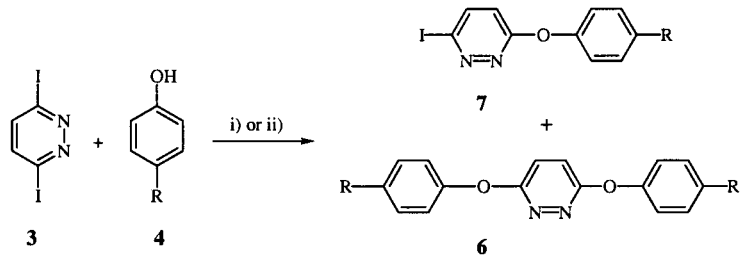
On the other hand, esterification of **3** with one equivalent of **4a** or **4c-4e** in the presence of potassium carbonate

afforded only 3-iodo-6-phenoxy derivatives **7a** or **7c-7e** in good yield, respectively. Reaction of **3** with one equivalent of **4b** and of potassium carbonate gave **6b** in 9% yield and **7b** in 62% yield. Whereas, treatment of **3** with two equivalents of **4** except for **4e** and of potassium carbonate yielded the corresponding 3,6-diphenoxy derivatives **7**. Compound **3** was reacted with **4e** (2 equivalents) and potassium carbonate (2 equivalents) to give only **7e** in 78% yield. We did not obtain compound **6e** from **3** and **4e** under our reaction lent) in methanol afforded **8c** (Method G) or **9b** (Method K). Treatment of **2** or **3** with potassium carbonate (2 equivalents) in methanol yielded **8d** (Method H and L). The structures of **8** and **9** were established by ir, nmr and elemental analyses.

The rates of the methoxylation and azidation of **2** are also faster than it is for **3** under the same conditions.

Further work including the biological activity and other chemical transformation of the products are under way in our laboratory.

Scheme III



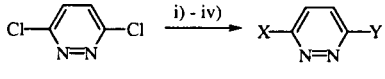
3 4

i) Method C; Phenol (1 equivalent), K_2CO_3 (1 equivalent), CH_3CN (or dimethylformamide).
ii) Method D; Phenol (2 equivalents), K_2CO_3 (2 equivalents), CH_3CN (or dimethylformamide).

R	OMe		Cl		NH_2		CN		NO_2	
	7a	**6a**	**7b**	**6b**	**7c**	**6c**	**7d**	**6d**	**7e**	**6e**
Method C	83	—	62	9	88	—	98	—	80	—
Method D	—	62	—	76	—	80	—	94	78	—

conditions. These results may also be due to the electron-withdrawal of the nitro group on the phenyl ring. According to our observation, the reaction of 3,6-dichloropyridazine (**2**) with 4-substituted-phenols **4** is faster than that of 3,6-diiodopyridazine (**3**) under our experimental conditions. According to our observation, the reactivity of 3,6-dihalopyridazines **2** or **3** is lower than it of 3-halo-6-phenoxy derivatives **5** and **7**. The structures of **5**, **6** and **7** were established by ir, nmr and elemental analyses.

Scheme IV



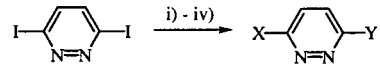
2 8

i) Method E; NaN_3, MeOH, reflux. ii) Method F; NaN_3, EtOH, reflux.
iii) Method G; MeOH, K_2CO_3 (1 equivalent), reflux.
iv) Method H; MeOH, K_2CO_3 (2 equivalents), reflux.

8	**a**	**b**	**c**	**d**
X	OMe	Cl	Cl	OMe
Y	N_3	N_3	OMe	OMe
Method	E	F	G	H
Yield (%)	61	60	82	68

Azidation of **2** or **3** with sodium azide in methanol gave **8a** (Method E and I), whereas reaction of **2** or **3** with sodium azide in ethanol gave **8b** (Method F) or **9a** (Method J). Methoxylation of **2** or **3** with potassium carbonate (1 equiva-

Scheme V



3 8a, 8d, 9

i) Method I; NaN_3, MeOH, reflux. ii) Method J; NaN_3, EtOH, reflux.
iii) Method K; MeOH, K_2CO_3 (1 equivalent), reflux.
iv) Method L; MeOH, K_2CO_3 (2 equivalents), reflux.

	8a	**9a**	**9b**	**8d**
X	OMe	I	I	OMe
Y	N_3	N_3	OMe	OMe
Method	I	J	K	L
Yield (%)	63	17	48	56

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover capillary apparatus and are uncorrected. Magnetic resonance spectra were obtained on a Varian Unity Plus 300 or a Bruker FTNMR-DRX 500 spectrometer with chemical shift values reported in δ units (part per million) relative to an internal standard (tetramethylsilane). Infrared spectral data were obtained on a Hitachi 270-50 spectrophotometer. Elemental analyses were performed with a Perkin Elmer 240C. Open-bed chromatography was carried out on silica gel 60 (70-230 mesh, Merck) using gravity flow. The column was packed as slurries with the elution solvent.

Table 1
Yields, Melting Points and Infrared Spectral Data of **3**, **5-9**

Compound No.	Method	Yield (%)	mp (°) (lit. mp)	IR (Potassium bromide) (cm^{-1})
3		75	170-171 (157-158) [17]	3100, 3005, 1630, 1540, 1380, 1160, 1100, 1025, 1000, 860, 740
5a	A	80	102-105	3075, 3025, 2960, 2910, 2850, 1620, 1600, 1520, 1470, 1330, 1300, 1250, 1200, 1140, 1110, 1080, 1040
5b	A	88	124-126	3100, 1600, 1510, 1440, 1350, 1310, 1280, 1220, 1190, 1160, 1040
5c	A	95	86-88	3500, 3400, 3250, 3100, 1650, 1630, 1600, 1530, 1430, 1350, 1300, 1210, 1160, 1100
5d	A	62	179-180	3100, 2250, 1620, 1590, 1560, 1520, 1440, 1340, 1300
	B	79		
5e	A	61	127-130	3100, 1630, 1610, 1590, 1540, 1500, 1420
	B	69		
6a	B	70	173-174	3100, 3050, 3000, 2950, 2875, 1630, 1520, 1450, 1360, 1320,
	D	72		1280, 1260, 1210, 1110, 1050, 1010
6b	A	2	191-192	3100, 1500, 1450, 1360, 1270,
	B	83		1200, 1170, 1100, 1010
	C	9		
	D	76		
6c	B	87	200-202	3450, 3350, 3250, 3125, 1660, 1540, 1460, 1380, 1280, 1220,
	D	80		1150, 1110, 1060, 1040
6d	D	94	198-200	3100, 2250, 1620, 1520, 1440, 1370, 1350, 1270, 1220, 1180, 1110, 1040
7a	C	83	107-108	3100, 2950, 2900, 1620, 1600, 1520, 1480, 1430, 1340, 1320, 1260, 1200, 1140, 1070, 1050
7b	C	62	119-120	3100, 1580, 1510, 1430, 1340, 1300, 1200
7c	C	88	126-127	3450, 3350, 3250, 3100, 2950, 2900, 1630, 1600, 1530, 1430, 1340, 1290, 1220
7d	C	98	203-204	3100, 2260, 1630, 1590, 1530, 1440, 1320, 1300, 1240, 1190, 1140
7e	C	80	136-138	3150, 3100, 1640, 1620, 1590, 1540, 1520, 1440, 1380, 1360,
	D	78		1340, 1320, 1230, 1190, 1140
8a	E	58	156-158 (155-157)	3075, 2275, 2225, 2150, 1620, 1560, 1510, 1480, 1380, 1340,
	I	38	[18]	1300, 1250, 1170, 1140, 1090, 1000
8b	F	60	128-130 (108-109) [18]	3075, 2275, 2225, 2150, 1620, 1550, 1470, 1380, 1340, 1300, 1250, 1170, 1140, 1080, 1000
8c	G	82	90-92	3075, 3000, 2950, 2900, 1600, 1470, 1410, 1340, 1320, 1200, 1180, 1160, 1080, 1020
8d	H	68	106-108	3100, 3050, 3000, 2900, 1640, 1600, 1500, 1460, 1420, 1370,
	L	56		1280, 1180, 1100, 1020
9a	J	17	119-120	3100, 2275, 2150, 1620, 1560, 1510, 1480, 1390, 1380, 1340, 1300, 1250, 1170, 1130, 1080, 1040, 1000, 970, 850

Table 1 (continued)

Compound No.	Method	Yield (%)	mp (°) (lit. mp)	IR (Potassium bromide) (cm^{-1})
9b	K	48	103-104 (104-105) [17]	3075, 2950, 2900, 1620, 1590, 1520, 1480, 1410, 1310, 1020

Table 2
^{1}H NMR Spectral Data of **3**, **5-9**

Compound No.	Solvent [a]	^{1}H NMR (δ, ppm)
3	C	7.42 (s, 2H)
5a	C	3.83 (s, 3H), 6.95 (d, 2H, J = 9.0), 7.14 (d, 1H, J = 9.3), 7.30 (d, 2H, J = 9.0), 7.48 (d, 1H, J = 9.3)
5b	C	7.18 (d, 2H, J = 8.8), 7.20 (d, 1H, J = 9.3), 7.40 (d, 2H, J = 8.9), 7.52 (d, 1H, J = 9.2)
5c	C	3.20 (bs, 2H), 6.63 (d, 2H, J = 8.7), 6.90 (d, 2H, J = 8.7), 7.01 (d, 1H, J = 9.1), 7.36 (d, 1H, J = 9.2)
5d	C	7.26 (d, 1H, J = 9.1), 7.38 (d, 2H, J = 8.7), 7.59 (d, 1H, J = 9.1), 7.75 (d, 2H, J = 8.8)
5e	C	7.30 (d, 1H, J = 9.1), 7.40 (d, 2H, J = 10.2), 7.64 (d, 1H, J = 8.9), 8.30 (d, 2H, J = 10.5)
6a	C	3.70 (s, 6H), 6.80 (d, 4H, J = 9.0), 7.06 (d, 4H, J = 9.0), 7.09 (s, 2H)
6b	C	7.07 (d, 4H, J = 8.8), 7.18 (s, 2H), 7.26 (d, 4H, J = 8.8)
6c	C	3.51 (bs, 4H), 6.59 (d, 2H, J = 8.7), 6.90 (d, 2H, J = 8.8), 7.05 (s, 2H)
6d	C	7.27 (d, 4H, J = 8.8), 7.30 (s, 2H), 7.62 (d, 4H, J = 8.8)
7a	C	3.81 (s, 3H), 6.83 (d, 1H, J = 9.1), 6.92 (d, 2H, J = 9.0), 7.10 (d, 2H, J = 9.0), 7.74 (d, 1H, J = 9.1)
7b	C	6.82 (d, 1H, J = 9.0), 7.08 (d, 2H, J = 6.7), 7.30 (d, 2H, J = 6.7), 7.72 (d, 1H, J = 9.1)
7c	C	3.66 (s, 2H), 6.69 (d, 2H, J = 8.6), 6.80 (d, 1H, J = 9.1), 6.96 (d, 2H, J = 8.6), 7.71 (d, 1H, J = 9.1)
7d	C	6.79 (d, 1H, J = 8.9), 7.27 (d, 2H, J = 8.7), 7.65 (d, 2H, J = 8.7), 7.78 (d, 1H, J = 9.3)
7e	C	6.92 (d, 1H, J = 9.0), 7.32 (d, 2H, J = 9.2), 7.80 (d, 1H, J = 9.1), 8.23 (d, 2H, J = 9.1)
8a	C	4.71 (s, 3H), 7.16 (d, 1H, J = 9.5), 8.34 (d, 1H, J = 9.6)
8b	C	7.07 (d, 1H, J = 9.5), 8.27 (d, 1H, J = 9.6)
8c	C	4.12 (s, 3H), 6.95 (d, 1H, J = 9.2), 7.35 (d, 1H, J = 9.2)
8d	C	4.05 (s, 6H), 6.91 (s, 2H)
9a	C	7.11 (d, 1H, J = 9.5), 8.32 (d, 1H, J = 9.5)
9b	C	3.87 (s, 3H), 6.46 (d, 1H, J = 9.1), 7.42 (d, 1H, J = 9.1)

[a] Solvent, C = Deuteriochloroform. [b] Abbreviations used, s = singlet, d = doublet, bs = broad singlet, J = in Hertz unit.

Table 3
^{13}C NMR Data of **3**, **5-9**

Compound No.	Solvent [a]	^{13}C NMR (δ, ppm)
3	C	124.2, 139.0
5a	C	56.0, 115.3, 120.1, 122.4, 131.8, 146.8, 152.2, 157.6, 165.8
5b	C	120.6, 123.1, 130.4, 131.5, 132.2, 152.0, 152.9, 165.3
5c	C	116.4, 119.9, 122.3, 131.6, 144.6, 145.6, 152.0, 166.1
5d	C	110.0, 118.0, 120.0, 122.5, 132.5, 135.0, 153.0, 157.0, 164.5
5e	C	119.5, 120.3, 124.1, 130.7, 143.7, 152.0, 156.6, 162.9
6a	C	56.0, 115.1, 121.9, 122.6, 147.5, 157.3, 163.7
6b	C	124.4, 124.9, 132.0, 132.9, 154.2, 165.3
6c	C	114.2, 119.4, 120.4, 141.9, 144.1, 161.6
6d	C	100.1, 109.5, 122.3, 123.1, 134.4, 157.1, 163.0
7a	C	56.1, 115.3, 118.1, 119.1, 122.4, 140.3, 146.8, 157.6, 166.4
7b	C	118.7, 119.5, 122.9, 130.2, 131.4, 140.6, 151.8, 165.7
7c	C	114.5, 115.9, 117.0, 120.4, 138.3, 142.7, 143.5, 164.7
7d	C	108.2, 117.1, 117.9, 118.3, 120.8, 132.9, 139.5, 155.1, 163.6
7e	C	119.6, 119.9, 121.9, 126.0, 141.1, 146.0, 158.1, 165.1
8a	C	56.6, 120.7, 120.9, 126.8, 155.3
8b	C	120.9, 126.8, 142.3, 155.3
8c	C	55.2, 120.0, 130.7, 151.1, 164.5
8d	C	54.6, 121.3, 162.0
9a	C	120.4, 126.4, 141.9, 154.9
9b	C	55.4, 117.2, 119.5, 139.6, 165.2

[a] Solvent, C = Deuteriochloroform.

Table 4

Elemental Analytical Data of **3-12**

Compound No.	Molecular Formula	Calcd./Found (%) C	H	N
3	$C_4H_2N_2I_2$	14.48	0.61	8.44
		14.68	0.71	8.59
5a	$C_{11}H_9N_2O_2Cl$	55.83	3.83	11.84
		55.86	4.03	12.03
5b	$C_{10}H_6N_2OCl_2$	49.82	2.51	11.62
		49.98	2.57	11.52
5c	$C_{10}H_8N_3OCl$	54.19	3.64	18.96
		54.33	3.86	18.98
5d	$C_{15}H_6N_3OCl$	57.04	2.61	18.14
		56.90	2.61	18.02
5e	$C_{10}H_6N_3O_3Cl$	47.73	2.40	16.70
		48.00	2.61	16.91
6a	$C_{18}H_{16}N_2O_4$	66.66	4.97	8.64
		66.86	5.01	8.87
6b	$C_{16}H_{10}N_2O_2Cl_2$	57.68	3.03	8.41
		57.78	3.11	8.65
6c	$C_{16}H_{14}N_4O_2$	65.30	4.79	19.04
		65.57	5.00	18.97
6d	$C_{18}H_{10}N_4O_2$	68.79	3.21	17.83
		68.83	3.40	17.99
7a	$C_{11}H_9N_2O_2I$	40.27	2.76	8.54
		40.34	2.85	8.67
7b	$C_{10}H_6N_2OClI$	36.12	1.82	8.42
		36.07	1.93	8.69
7c	$C_{10}H_8N_3OI$	38.36	2.58	13.42
		38.55	2.61	13.59
7d	$C_{11}H_6N_3OI$	40.89	1.87	13.01
		40.99	1.90	12.92
7e	$C_{10}H_6N_3O_3I$	35.01	1.76	12.25
		35.20	2.00	12.47
8a	$C_5H_5N_5O$	39.74	3.33	46.34
		39.87	3.60	46.58
8b	$C_4H_2N_5Cl$	30.89	1.30	45.02
		30.96	1.59	45.18
8c	$C_5H_5N_2OCl$	41.54	3.49	19.38
		41.64	3.67	19.44
8d	$C_6H_8N_2O_2$	51.42	5.75	19.99
		51.74	5.82	20.07
9a	$C_4H_2N_5I$	19.45	0.82	28.35
		19.71	0.97	28.60
9b	$C_5H_5N_2OI$	25.45	2.14	11.87
		25.51	2.40	11.90

3,6-Diiodopyridazine (**3**).

A mixture of **2** (10 g, 67.13 mmoles), hydriodic acid (40 ml, 55%) and iodine monochloride (5.5 g, 33.87 mmoles) was reacted for 24 hours at 70°. After cooling to room temperature, the mixture was poured into ice water (300 ml) with stirring. The solution was neutralized by aqueous potassium hydroxide (20%, 120 ml). After the precipitate was filtered, the resulting residue was washed with water (1000 ml), with aqueous sodium thiosulfate (10%, 50 ml) and then with *n*-hexane (10 ml). The residue was recrystallized from ethyl acetate to give **3** in 75% (16.69 g).

3-Chloro-6-(4-methoxyphenonoxy)pyridazine (**5a**).

Method A.

After stirring a solution of *p*-methoxyphenol (**4a**, 1 g, 8.05 mmoles), potassium carbonate (1.11 g, 8.05 mmoles) and acetonitrile (30 ml) for 10 minutes, **2** (1 g, 6.71 mmoles) was added. The reaction mixture was refluxed for 9.5 hours. After cooling to room temperature, the solvent was evaporated under reduced pressure. Water (50 ml) was added to the residue. The product was then extracted with chloroform (50 ml x 3) and dried over anhydrous magnesium sulfate. After evaporating the solvent under reduced pressure, the resulting residue was recrystallized from chloroform to give **5a** in 80% (1.27 g) yield.

3-Chloro-6-(4-chlorophenoxy)pyridazine (**5b**) and 3,6-Di-(4-chlorophenoxy)pyridazine (**6b**).

Method A.

A mixture of *p*-chlorophenol (**4b**, 1.52 g, 11.84 mmoles), potassium carbonate (1.64 g, 11.84 mmoles), acetonitrile (40 ml) and **2** (1.47 g, 9.87 mmoles) was refluxed for 7 hours. After evaporating the solvent under reduced pressure, water (50 ml) was added with stirring. The product was extracted with chloroform (50 ml x 3) and dried over anhydrous magnesium sulfate. The filtrate was co-evaporated with silica gel (1 g) under reduced pressure. The residue was applied to the top of an open-bed silica gel column (2.5 x 7 cm). The column was eluted with chloroform/ethyl acetate (10:1, v/v). The fractions containing **5b** (Rf = 0.44, chloroform/ethyl acetate = 10:1, v/v) were combined and evaporated under reduced pressure to give **5b** in 88% (2.08 g) yield. The fractions containing **6b** (Rf = 0.66, chloroform/ethyl acetate = 10:1, v/v) were combined and evaporated under reduced pressure to give **6b** in 2% (0.05 g) yield.

3-Chloro-6-(4-aminophenoxy)pyridazine (**5c**).

Method A.

A solution of *p*-aminophenol (**4c**, 0.44 g, 4.03 mmoles), potassium carbonate (0.56 g, 4.03 mmoles), potassium fluoride (0.23 g, 4.03 mmoles), **2** (0.5 g, 3.36 mmoles) and acetonitrile (40 ml) was refluxed for 25.5 hours. After evaporating the solvent under reduced pressure, water (30 ml) and chloroform (30 ml) were added with stirring. The chloroform layer was separated, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was recrystallized from ethyl acetate to give **5c** in 95% (0.71 g) yield.

3-Chloro-6-(4-cyanophenoxy)pyridazine (**5d**).

Method A.

A solution of *p*-cyanophenol (**4d**, 0.96 g, 8.05 mmoles), potassium carbonate (1.11 g, 8.05 mmoles), **2** (1 g, 6.71 mmoles) and dimethylformamide (30 ml) was refluxed for 5.5 hours. After cooling to room temperature, water (50 ml) and chloroform (50 ml) were added with stirring. The chloroform layer was separated, dried over anhydrous magnesium sulfate and coevaporated with silica gel (1 g) under reduced pressure. The residue was applied to the top of an open-bed silica gel column (2.5 x 7 cm). The column was eluted with ethyl acetate/*n*-hexane (1:10, v/v). The fractions containing the product were combined and evaporated under reduced pressure to give **5d** in 62% (0.96 g) yield.

Method B.

A mixture of *p*-cyanophenol (2.64 g, 22.15 mmoles), potassium carbonate (3.06 g, 22.15 mmoles), **2** (1.5 g, 10.07 mmoles) and dimethylformamide (20 ml) was refluxed for 0.2 hours. After cooling to room temperature, water (100 ml) and chloroform (100 ml) were added to the mixture with stirring. The chlo-

roform layer was separated, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was applied to the top of an open-bed silica gel column. The column was eluted with ethyl acetate/*n*-hexane (1:2, v/v). The fractions containing **5d** (Rf = 0.22, ethyl acetate/*n*-hexane = 1:2, v/v) were combined and evaporated under reduced pressure to give **5d** in 79% (1.84 g) yield.

3-Chloro-6-(4-nitrophenoxy)pyridazine (**5e**).

Method A.

A solution of *p*-nitrophenol (**4e**, 3.36 g, 24.17 mmoles), potassium carbonate (3.34 g, 24.17 mmoles), **2** (3 g, 20.14 mmoles) and dimethylformamide (30 ml) was refluxed for 4 hours. After cooling to room temperature, water (50 ml) and chloroform (50 ml) were added with stirring. The chloroform layer was separated, dried over anhydrous magnesium sulfate and co-evaporated with silica gel (1.5 g) under reduced pressure. The residue was applied to the top of an open-bed silica gel column (2.5 x 7 cm). The column was eluted with ethyl acetate/*n*-hexane (1:5, v/v). The fractions containing the product were combined and evaporated under reduced pressure to give **5e** in 61% (3.1 g) yield.

Method B.

A mixture of *p*-nitrophenol (0.7 g, 5.02 mmoles), potassium carbonate (0.69 g, 5.02 mmoles), **2** (0.34 g, 2.28 mmoles) and dimethylformammide (20 ml) was refluxed for 1.2 hours. After cooling to room temperature, water (100 ml) and chloroform (50 ml) were added to the mixture with stirring. The chloroform layer was separated, dried over anhydrous magnesium sulfate and evaporated under reduced pressure to give the crude product. The crude product was recrystallized from diethyl ether to afford **5e** in 69% (0.4 g) yield.

3,6-Di-(4-methoxyphenoxy)pyridazine (**6a**).

Method B.

A solution of *p*-methoxyphenol (**4a**, 1.83 g, 14.76 mmoles), potassium carbonate (2.04 g, 14.76 mmoles), **2** (1 g, 6.71 mmoles) and dimethylformamide (20 ml) was refluxed for 4.5 hours. After cooling to room temperature, a solution of water/chloroform (150 ml; 2:1, v/v) was added with stirring. The chloroform layer was separated, dried over anhydrous magnesium sulfate and co-evaporated with silica gel (1.5 g) under reduced pressure. The residue was applied to the top of an open-bed silica gel column (2.5 x 6 cm). The column was eluted with ethyl acetate/*n*-hexane (1:8, v/v). The fractions containing the product were combined and evaporated under reduced pressure to give **6a** in 70% (1.53 g) yield.

Method D.

After stirring a solution of *p*-methoxyphenol (**4a**, 0.48 g, 3.85 mmoles), potassium carbonate (0.53 g, 3.85 mmoles) and dimethylformamide (20 ml) for 10 minutes at room temperature, **3** (0.58 g, 1.75 mmoles) was added. The mixture was refluxed for 3 hours. After cooling to room temperature, water/chloroform (100 ml; 1:1, v/v) were added with stirring. The chloroform layer was separated, dried over anhydrous magnesium sulfate and co-evaporated with silica gel (1.5 g) under reduced pressure. The residue was applied to the top of an open-bed silica gel column (3 x 10 cm). The column was eluted with ethyl acetate/*n*-hexane (1:4, v/v). The fractions containing the product were combined and evaporated under reduced pressure to give **6a** in 62% (0.35 g) yield.

3,6-Di-(4-chlorophenoxy)pyridazine (**6b**).

Method B.

After stirring a solution of *p*-chlorophenol (**4b**, 1.9 g, 14.76 mmoles), potassium carbonate (2.04 g, 14.76 mmoles) and acetonitrile (30 ml) for 10 minutes at room temperature, **2** (1 g, 6.71 mmoles) was added. The mixture was refluxed for 4.7 days. After cooling to room temperature, the solvent was evaporated under reduced pressure. A solution of water/chloroform (50 ml, 1:1, v/v) was added to the residue with stirring. The chloroform layer was separated, dried over anhydrous magnesium sulfate and co-evaporated with silica gel (1 g) under reduced pressure. The residue was applied to the top of an open-bed silica gel column (2 x 5 cm). The column was eluted with ethyl acetate/chloroform (1:20, v/v). The fractions containing the product were combined and evaporated under reduced pressure. The residue was recrystallized from ethyl acetate to give **6b** in 83% (1.85 g) yield.

Method D.

After stirring a solution of *p*-chlorophenol (**4b**, 0.43 g, 3.32 mmoles), potassium carbonate (0.46 g, 3.32 mmoles) and acetonitrile (30 ml) for 10 minutes at room temperature, **3** (0.5 g, 1.51 mmoles) was added. The mixture was refluxed for 9 days. After cooling to room temperature, the solvent was evaporated under reduced pressure. Water (50 ml) was added to the residue with stirring. The precipitate was washed with water (300 ml), then washed with diethyl ether (10 ml) and dried in air to give **6b** in 76% (0.38 g) yield.

3,6-Di-(4-aminophenoxy)pyridazine (**6c**).

Method B.

After stirring a solution of *p*-aminophenol (**4c**, 1.61 g, 14.76 mmoles), potassium carbonate (2.04 g, 14.76 mmoles) and acetonitrile (40 ml) for 10 minutes at room temperature, **2** (1 g, 6.71 mmoles) was added. The mixture was refluxed for 87 hours. After cooling to room temperature, the solvent was evaporated under reduced pressure. Water (50 ml) was added to the residue with stirring. The resulting precipitate was filtered, then washed with water (50 ml x 2) and dried in air to give **6c** in 87% (1.75 g) yield.

Method D.

After stirring a solution of *p*-aminophenol (**4c**, 0.36 g, 3.32 mmoles), potassium carbonate (0.46 g, 3.32 mmoles) and dimethylformamide (20 ml) for 10 minutes at room temperature, **3** (0.5 g, 1.51 mmoles) was added. The mixture was refluxed for 46 hours. After cooling to room temperature, the solvent was evaporated under reduced pressure. Water (50 ml) was added to the residue with stirring. The precipitate was washed with water (200 ml), then washed with diethyl ether (10 ml) and dried in air to give **6c** in 80% (0.36 g) yield.

3,6-Di-(4-cyanophenoxy)pyridazine (**6d**).

Method D.

After stirring a solution of *p*-cyanophenol (**4d**, 0.79 g, 6.62 mmoles), potassium carbonate (0.91 g, 6.62 mmoles) and acetonitrile (30 ml) for 10 minutes at room temperature, **3** (1 g, 3.01 mmoles) was added. The mixture was refluxed for 7.3 days.

After cooling to room temperature, the solvent was evaporated under reduced pressure. A solution of water/chloroform (50 ml, 1:1, v/v) was added to the residue with stirring. The chloroform layer was separated, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was recrystallized from chloroform and dried in air to give **6d** in 94% (0.89 g) yield.

3-Iodo-6-(4-methoxyphenoxy)pyridazine (**7a**).

Method C.

After stirring a mixture of *p*-methoxyphenol (**4a**, 1.62 g, 13.02 mmoles), potassium carbonate (1.8 g, 13.02 mmoles) and acetonitrile (40 ml) for 10 minutes at room temperature, **3** (3.6 g, 10.85 mmoles) was added to the solution. The mixture was refluxed for 42 hours. After evaporating the solvent under reduced pressure, water (60 ml) was added with stirring. The resulting precipitate was washed with water (300 ml), then washed with diethyl ether (10 ml) and dried in air to give **7a** in 83% (2.95 g) yield.

3-Iodo-6-(4-chlorophenoxy)pyridazine (**7b**) and 3,6-Di-(4-chlorophenoxy)pyridazine (**6b**).

Method C.

After stirring a mixture of *p*-chlorophenol (**4b**, 1.4 g, 10.85 mmoles), potassium carbonate (1.5 g, 10.85 mmoles) and acetonitrile (40 ml) for 10 minutes at room temperature, **3** (3 g, 9.04 mmoles) was added to the solution. The mixture was refluxed for 48.5 hours. After evaporating the solvent under reduced pressure, water (100 ml) was added with stirring. The products were extracted with chloroform (50 ml x 3) and dried over anhydrous magnesium sulfate. The solvent was co-evaporated with silica gel (2 g) under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column (2.5 x 10 cm). The column was eluted with chloroform/ethyl acetate (50:1, v/v). The fractions containing **6b** (Rf = 0.74, chloroform/ethyl acetate = 10:1, v/v) were combined and evaporated under reduced pressure. The residue was recrystallized from ethyl acetate and dried in air to give **6b** in 9% (0.27 g) yield. The fractions containing **7b** (Rf = 0.68, chloroform/ethyl acetate = 10:1, v/v) were combined and evaporated under reduced pressure. The residue was recrystallized from ethyl acetate and dried in air to give **7b** in 62% (1.85 g) yield.

3-Iodo-6-(4-aminophenoxy)pyridazine (**7c**).

Method C.

After stirring a mixture of *p*-aminophenol (**4c**, 1.18 g, 10.85 mmoles), potassium carbonate (1.5 g, 10.85 mmoles) and acetonitrile (40 ml) for 10 minutes at room temperature, **3** (3 g, 9.04 mmoles) was added to the solution. The mixture was refluxed for 68 hours. After evaporating the solvent under reduced pressure, water (60 ml) was added with stirring. The resulting precipitate was washed with water (300 ml) and dried in air to give **7c** in 88% (2.49 g) yield.

3-Iodo-6-(4-cyanophenoxy)pyridazine (**7d**).

Method C.

After stirring a mixture of *p*-cyanophenol (**4d**, 1.29 g, 10.85 mmoles), potassium carbonate (1.5 g, 10.85 mmoles) and acetonitrile (40 ml) for 10 minutes at room temperature, **3** (3 g, 9.04 mmoles) was added to the solution. The mixture was refluxed for 48 hours. After evaporating the solvent under reduced pressure, water (50 ml) and chloroform (50 ml) were added with stirring. The chloroform layer was separated and dried over anhydrous magnesium sulfate. The resulting solution was evaporated under reduced pressure. The residue was recrystallized from ethyl acetate and dried in air to give **7d** in 98% (2.87 g) yield.

3-Iodo-6-(4-nitrophenoxy)pyridazine (**7e**)

Method C.

After stirring a mixture of *p*-nitrophenol (**4e**, 0.5 g, 3.61 mmoles), potassium carbonate (0.5 g, 3.61 mmoles) and dimethylformamide (20 ml) for 10 minutes at room temperature, **3** (1 g, 3.01 mmoles) was added to the solution. The mixture was refluxed for 4.5 hours. After cooling to room temperature, the solution was poured into water (300 ml) with stirring. The resulting precipitate was washed with water (200 ml), then washed with diethyl ether (10 ml) and dried in air to give **7e** in 80% (0.83 g) yield.

Method D.

A mixture of *p*-nitrophenol (0.92 g, 6.62 mmoles), potassium carbonate (9.15 g, 6.62 mmoles), **3** (1 g, 3.01 mmoles) and dimethylformamide (20 ml) was refluxed for 3 hours. After cooling to room temperature, water (50 ml) and chloroform (50 ml) were added to the mixture with stirring. The chloroform layer was separated, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The resulting residue was recrystallized from ethyl acetate to give **7e** in 78% (0.8 g) yield.

3-Azido-6-methoxypyridazine (**8a**).

Method E.

A mixture of **2** (2 g, 13.43 mmoles), sodium azide (1.05 g, 16.12 mmoles) and methanol (20 ml) was refluxed for 68 hours. After evaporating the solvent under reduced pressure, water (25 ml) and chloroform (25 ml) were added to the residue with stirring. The chloroform layer was separated and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column (3 x 7 cm). The column was eluted with ethyl acetate/*n*-hexane (1:4, v/v). The fractions containing the product were combined, evaporated under reduced pressure and dried in air to afford **8a** in 61% (1.23 g) yield.

Method I.

A mixture of **3** (1 g, 3.01 mmoles), sodium azide (0.23 g, 3.61 mmoles), and methanol (20 ml) was refluxed for 38.5 hours. After evaporating the solvent under reduced pressure, water and chloroform (25 ml) were added to the residue with stirring. The chloroform layer was separated and dried over anhydrous magnesium sulfate. The solution was co-evaporated with silica gel (1 g) under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column (2 x 7 cm). The column was eluted with chloroform/diethyl ether (10:1, v/v). The fractions containing the product were combined, evaporated under reduced pressure and dried in air to afford **8a** in 63% (0.29 g) yield. The starting material was also recovered in 0.18 g.

3-Azido-6-chloropyridazine (**8b**).

Method F.

A mixture of **2** (1 g, 6.71 mmoles), sodium azide (0.52 g, 8.05 mmoles), and ethanol (20 ml) was refluxed for 5 days. After

evaporating the solvent under reduced pressure, water (25 ml) and chloroform (25 ml) were added to the residue with stirring. The chloroform layer was separated and dried over anhydrous magnesium sulfate. The solvent was co-evaporated with silica gel (1 g) under reduced pressure. The resulting residue was applied to the top of an open-bed silica gel column (2 x 6 cm). The column was eluted with chloroform/*n*-hexane (1:1, v/v). The fractions containing the product were combined, evaporated under reduced pressure and dried in air to afford **8b** in 60% (0.62 g) yield.

3-Chloro-6-methoxypyridazine (**8c**).

Method G.

A mixture of **2** (1 g, 6.71 mmoles), potassium carbonate (1.11 g, 8.05 mmoles), and methanol (30 ml) was refluxed for 1 hour. After evaporating the solvent under reduced pressure, water (25 ml) and chloroform (25 ml) were added to the residue with stirring. The chloroform layer was separated and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The resulting residue was recrystallized from chloroform/*n*-hexane (2:1, v/v) and dried in air to afford **8c** in 82% (1.59 g) yield.

3,6-Dimethoxypyridazine (**8d**).

Method H.

A mixture of **2** (2 g, 13.43 mmoles), potassium carbonate (4.08 g, 29.55 mmoles), and methanol (30 ml) was refluxed for 8 days. After evaporating the solvent under reduced pressure, water (25 ml) and chloroform (25 ml) were added to the residue with stirring. The chloroform layer was separated and dried over anhydrous magnesium sulfate. The solvent was evaporated under reduced pressure. The resulting residue was recrystallized from ethyl acetate and dried in air to afford **8d** in 68% (1.28 g) yield.

Method L.

A mixture of **3** (2 g, 6.03 mmoles), potassium carbonate (1.83 g, 13.27 mmoles), and methanol (30 ml) was refluxed for 4 days. After evaporating the solvent under reduced pressure, water (50 ml) was added to the residue with stirring. The resulting precipitate was filtered and dried in air to afford **8d** in 56% (0.48 g) yield.

3-Azido-6-iodopyridazine (**9a**).

A solution of **3** (1 g, 3.01 mmoles), sodium azide (0.23 g, 3.61 mmoles), and ethanol (30 ml) was refluxed for 6 days. After evaporating the solvent under reduced pressure, water (25 ml) and chloroform (25 ml) were added with stirring. The chloroform layer was separated, dried over anhydrous magnesium sulfate and evaporated under reduced pressure. The residue was applied to the top of an open-bed silica gel column (3 x 7 cm). The column was eluted with chloroform/diethyl ether (10:1, v/v). The fractions containing the starting material **3**, (Rf = 0.75, chloroform/diethyl ether = 10:1, v/v) were combined and evaporated under reduced pressure to obtain **3** (0.29 g). The fractions containing the product (Rf = 0.45, chloroform/diethyl ether, 10:1, v/v) were combined, evaporated under reduced pressure and dried in air to afford **9a** in 17% (0.13 g) yield.

3-Iodo-6-methoxypyridazine (**9b**).

A mixture of **3** (0.5 g, 1.51 mmoles), potassium carbonate (0.25 g, 1.81 mmoles) and methanol (30 ml) was refluxed for 2 hours. After evaporating the solvent under reduced pressure, water (50 ml) was added to the residue with stirring. The resulting precipitate was filtered and dried in air to yield **9b** in 48% (0.17 g) yield.

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