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Site-Selectivity in the Reaction of 3-Substituted Pyridine 1-Oxides with Phosphoryl Chloride

HIROSHI YAMANAKA,* TOMIO ARAKI, and TAKAO SAKAMOTO

*Pharmaceutical Institute, Tohoku University,
Aobayama, Sendai 980, Japan*

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Site-selectivity in the reaction of 3-substituted pyridine 1-oxide with phosphoryl chloride was investigated. When a strongly electron-withdrawing group (e.g. CN, CONRR', COOR, or NO₂) was substituted at the 3-position, the reaction of 3-substituted pyridine 1-oxides with phosphoryl chloride yielded 3-substituted 2-chloropyridines as the main products.

Keywords—site-selectivity; 3-substituted pyridine 1-oxide; phosphoryl chloride; 3-substituted 2-chloropyridine; chlorination

In the previous paper,¹⁾ we have reported that the reaction of some pyridine 1-oxides, which contain a 3-substituent having lone-pair electrons conjugated with the π -electrons of the pyridine ring, with trimethylsilyl cyanide proceeds site-selectively. For example, the reaction of 3-halopyridine 1-oxides with trimethylsilyl cyanide in acetonitrile in the presence of triethylamine gave 3-halo-2-pyridinecarbonitriles predominantly. The reaction of pyridine 1-oxides with phosphoryl chloride, like the reaction with trimethylsilyl cyanide, is considered to proceed through an ionic addition-elimination mechanism. Therefore, our interest was focussed next on the reaction of 3-substituted pyridine 1-oxides with phosphoryl chloride, in the anticipation of synthetically utilizable site-selectivity.

Prior to our present investigation, the following results have been reported in the literature.

1) The reaction of 3-methylpyridine 1-oxide with phosphoryl chloride gave a mixture of 2-chloro-3-methylpyridine, 2-chloro-5-methylpyridine, and 4-chloro-3-methylpyridine.²⁾

2) 3-Carbamoylpyridine 1-oxide was transformed into 2-chloro-3-pyridinecarbonitrile exclusively by the reaction of phosphoryl chloride and phosphorus pentachloride, although the yield of the product was unsatisfactory (35—39%).³⁾

3) The reaction of 3-nitropyridine 1-oxide with phosphoryl chloride⁴⁾ gave 2-chloro-3-nitropyridine (30%) together with a small amount (8.4%) of 2-chloro-5-nitropyridine.⁵⁾

In order to observe the substituent effect in the reaction of 3-substituted pyridine 1-oxides with phosphoryl chloride, the reaction conditions were arranged as follows. 3-Substituted pyridine 1-oxides (**1a—l**) (10 mmol) were heated with excess phosphoryl chloride (10 ml) at 110°C for 2 h, and the ratio of the crude products was analyzed with the aid of gas-chromatography (GC). Structural identification of the products was done by proton nuclear magnetic resonance (¹H-NMR) spectroscopy and by GC using products isolated from the reaction mixture or authentic synthetic specimens.

Based on the results shown in Table I, it is concluded that the reaction of 3-substituted pyridine 1-oxides with phosphoryl chloride can be adopted for the synthesis of 2-chloropyridines which have an electron-withdrawing group at the 3-position, although the substituent effect in the chlorination is different from that in the cyanation with trimethylsilyl cyanide.

For example, ethyl 2-chloro-3-pyridinecarboxylate (**2f**) was isolated in a pure state by

TABLE I. Reaction of 3-Substituted Pyridine 1-Oxides with Phosphoryl Chloride

$$\text{1a-I} \xrightarrow{\text{POCl}_3} \text{2a-I} + \text{3a-I} + \text{4a-I}$$

Substrate 1	Yield (%)	Product ratio (%) of determined by GC		
		2	3	4
a (R=H)	82	70	—	30
b (R=CN)	83	88	10	2
c (R=CONH ₂)	69 ^{a)}	86	12	2
d (R=CONEt ₂)	93	80	20	0
e (R=COOH)	75 ^{b)}	86	14	0
f (R=COOEt)	93	80	20	0
g (R=NO ₂)	68	73	27	0
h (R=Cl)	74	47	38	15
i (R=Br)	77	46	46	8
j (R=Me)	77	30	27	43
k (R=Ph)	84	32	46	22
l (R=NMe ₂)	80	34	47	19

a) Products were chloropyridine-3-carbonitriles. b) Products were isolated as ethyl chloropyridine-3-carboxylates.

simple column chromatography of the product derived from 3-ethoxycarbonylpyridine 1-oxide (**1f**). Furthermore, the reaction of 3-carbamoylpyridine 1-oxide (**1c**) with phosphoryl chloride alone gave 2-chloro-3-pyridinecarbonitrile (**2b**) in 59% yield.⁶⁾ In this case, recrystallization after decolorization through a short alumina column is enough for removal of the by-products (**3b** and **4b**).

Experimental

All melting points and boiling points are uncorrected. Gas-chromatograms were obtained with a Shimadzu GC-4CM using a column packed with SE-30. ¹H-NMR spectra were taken at 60 MHz with a JEOL JNM-PMX 60 spectrometer. Chemical shifts are expressed in δ (ppm) values, and coupling constants are expressed in hertz (Hz). The following abbreviations are used: s=singlet, d=doublet, dd=double doublet, and m=multiplet.

Starting pyridine 1-oxides were synthesized according to the literature¹⁾ and references cited therein.

General Procedure for the Reaction of 3-Substituted Pyridine 1-Oxides with Phosphoryl Chloride—A pyridine 1-oxide (10 mmol) was carefully added to POCl₃ (10 ml), and the mixture was heated at 110 °C for 2 h. After evaporation of the excess POCl₃, the residue was poured onto ice, made alkaline with aqueous NH₃, and extracted with CH₂Cl₂. The CH₂Cl₂ extract was purified by silica gel column chromatography.

Preparation of 2-Chloro-3-pyridinecarbonitrile (2b)—A mixture of 3-carbamoylpyridine 1-oxide (**1c**) (27.6 g, 0.2 mol) and POCl₃ (200 ml) was refluxed for 3.5 h. After evaporation of the excess POCl₃, the residue was poured onto ice, made alkaline with K₂CO₃, and extracted with CHCl₃. The CHCl₃ extract was purified by alumina column chromatography using C₆H₆ as an eluent. The C₆H₆ eluate gave colorless prisms which were recrystallized from cyclohexane. Yield 16.2 g (59%).

Preparation of Ethyl 2-Chloro-3-pyridinecarboxylate (2f)—A mixture of 3-ethoxycarbonylpyridine 1-oxide (**1f**) (33.4 g, 0.2 mol) and POCl₃ (200 ml) was refluxed for 5 h. After evaporation of the excess POCl₃, the residue was poured onto ice, made alkaline with K₂CO₃, and extracted with CHCl₃. The CHCl₃ extract was purified by silica gel column chromatography using hexane–Et₃N (9:1 v/v) as an eluent. The first eluate gave a mixture of ethyl 6-chloro-3-pyridinecarboxylate (**3f**) and impurities. The second eluate gave **2f** as a colorless liquid. Yield 17.8 g (48%).

2-Chloro-N,N-diethyl-3- (2d) and 2-Chloro-N,N-diethyl-5-pyridinecarboxamide (3d)—3-(N,N-Diethylcarbamoyl)pyridine 1-oxide (**1d**) (1.94 g, 10 mmol) was treated according to the general procedure. The first eluate

with hexane-Et₃N (9:1 v/v) gave **3d** as a colorless liquid. Yield 380 mg (18%). The second eluate gave **2d** as a colorless liquid. Yield 500 mg (24%).

3-(*N,N*-Diethylcarbamoyl)-4-nitropyridine 1-Oxide—A solution of ethyl chloroformate (10.8 g, 100 mmol) in dry tetrahydrofuran (150 ml) was added dropwise at -15°C to a mixture of 4-nitro-3-carboxypyridine 1-oxide (9.2 g, 50 mmol), Et₃N (10.1 g, 100 mmol), and dry dioxane (130 ml), and the mixture was stirred at -15°C for 3 h. Then, excess Et₂NH (21 ml) was added at 0°C , and the mixture was stirred at 0°C for 30 min. After removal of the solvent, the residue was extracted with acetone. The acetone extract gave a yellow solid (1.8 g), which was used in the next step without further purification.

4-Chloro-*N,N*-diethyl-3-pyridinecarboxamide (4d)—A mixture of 3-(*N,N*-diethylcarbamoyl)-4-nitropyridine 1-oxide (478 mg, 2 mmol) and AcCl (15 ml) was refluxed for 1 h. After evaporation of the excess AcCl, CHCl₃ (5 ml) and PCl₃ (550 mg, 4 mmol) were added to the residue. The mixture was refluxed for 2 h, made alkaline with 3 *N* Na₂CO₃, and extracted with CHCl₃. The CHCl₃ extract was distilled *in vacuo* to give a colorless liquid. Yield 400 mg (94%).

Ethyl 2-Chloro-5-pyridinecarboxylate (3f)—A mixture of 2-oxo-1,2-dihydro-5-pyridinecarboxylic acid (1.39 g, 10 mmol) and POCl₃ (10 ml) was refluxed for 30 min. After evaporation of the excess POCl₃, dry EtOH (10 ml) was added to the residue, and the mixture was stirred at room temperature overnight. After evaporation of the EtOH, the residue was made alkaline with K₂CO₃ and extracted with CHCl₃. The CHCl₃ extract was purified by silica gel column chromatography using C₆H₆-AcOEt (9:1 v/v) as an eluent to give a colorless liquid. Yield 1.3 g (70%).

2-Chloro-3- (2k), 2-Chloro-5- (3k), and 4-Chloro-3-phenylpyridine (4k)—3-Phenylpyridine 1-oxide (**1k**) (1.71 g, 10 mmol) was treated according to the general procedure. The first eluate with hexane-Et₃N (9:1 v/v) gave **3k** as a colorless solid. Yield 600 mg (31%). The second eluate gave **2k** as a colorless solid. Yield 420 mg (22%). The third eluate gave **4k** as a colorless liquid. Yield 240 mg (13%).

2-Chloro-3- (2l), 2-Chloro-5- (3l), and 4-Chloro-3-(*N,N*-dimethylamino)pyridine (4l)—*N,N*-Dimethylaminopyridine 1-oxide (**1l**) (1.37 g, 10 mmol) was treated according to the general procedure. The first eluate with C₆H₆ gave **4l** as a colorless liquid. Yield 150 mg (10%). The second eluate gave **3l** as colorless scales, which were recrystal-

TABLE II. Physical Constants and Spectral Data for Chloropyridines

No.	mp or bp/mmHg ($^{\circ}\text{C}$) (Lit. mp or bp/mmHg)	¹ H-NMR δ (ppm) (CDCl ₃) ring protons
2b	105 (105—106 ^{3l})	7.43 (1H, dd, $J=5, 8$), 8.03 (1H, dd, $J=2, 8$), 8.57 (1H, dd, $J=2, 5$)
3b	115—116 (117—118 ^{7l})	7.85 (1H, d, $J=6$), 7.97 (1H, dd, $J=2, 6$), 8.74 (1H, d, $J=2$)
4b	101—102 (102 ^{8l})	7.85 (1H, d, $J=6$), 8.83 (1H, d, $J=6$), 8.93 (1H, s)
2d	120—125/2	7.21 (1H, dd, $J=4, 6$), 7.50 (1H, dd, $J=2, 6$), 8.32 (1H, dd, $J=2, 4$)
3d	130—135/2	7.28 (1H, d, $J=4$), 7.64 (1H, dd, $J=2, 4$), 8.32 (1H, d, $J=2$)
4d	140/1	7.30 (1H, d, $J=5$), 8.36 (1H, s), 8.40 (1H, d, $J=5$)
2f	120—125/15 (78/0.1 ^{9l})	7.24 (1H, dd, $J=5, 8$), 8.08 (1H, dd, $J=2, 8$), 8.43 (1H, dd, $J=2, 5$)
3f	150/18	7.38 (1H, d, $J=8$), 8.20 (1H, dd, $J=2, 8$), 8.92 (1H, d, $J=2$)
4f	130—135/15 (85/1 ^{10l})	7.35 (1H, d, $J=5$), 8.55 (1H, d, $J=5$), 8.99 (1H, s)
2g	99—101 (96—98 ^{4l})	7.67 (1H, dd, $J=5, 8$), 8.16 (1H, dd, $J=2, 8$), 8.65 (1H, dd, $J=2, 5$)
3g	108—109 (110 ^{5l})	7.60 (1H, d, $J=8$), 8.50 (1H, dd, $J=2, 8$), 9.29 (1H, d, $J=2$)
4g	154—155 (156 ^{11l})	7.56 (1H, d, $J=4$), 8.69 (1H, d, $J=4$), 9.13 (1H, s)
2h	45—46 (46—47 ^{12l})	7.29 (1H, dd, $J=4, 8$), 7.80 (1H, dd, $J=2, 8$), 8.37 (1H, dd, $J=2, 4$)
3h	58—59 (60 ^{13l})	7.28 (1H, d, $J=8$), 7.82 (1H, dd, $J=2, 8$), 8.47 (1H, d, $J=2$)
4h	90/15 (22—23 ^{14l})	7.34 (1H, d, $J=3$), 8.36 (1H, d, $J=3$), 8.56 (1H, s)
2i	54—55 (55—56 ^{15l})	7.13 (1H, dd, $J=5, 8$), 7.97 (1H, dd, $J=2, 8$), 8.40 (1H, dd, $J=2, 5$)
3i	69 (67—69 ^{15l})	7.23 (1H, d, $J=8$), 7.79 (1H, dd, $J=2, 8$), 8.49 (1H, d, $J=2$)
4i	115/20 (196—198 ^{16l})	7.33 (1H, d, $J=5$), 8.37 (1H, d, $J=5$), 8.73 (1H, s)
2j	193 (192—193 ^{17l})	7.22 (1H, dd, $J=3, 8$), 7.57 (1H, dd, $J=2, 8$), 8.27 (1H, dd, $J=2, 3$)
3j	115/30 (56/2.5 ^{14l})	7.20 (1H, d, $J=8$), 7.50 (1H, dd, $J=2, 8$), 8.24 (1H, d, $J=2$)
4j	100—105/115 (159—160 ^{18l})	7.28 (1H, d, $J=5$), 8.37 (1H, d, $J=5$), 8.46 (1H, s)
2k	46—47	7.20 (1H, dd, $J=5, 7$), 7.57 (1H, dd, $J=2, 7$), 8.21 (1H, dd, $J=2, 5$)
	110—115/3	
3k	62—63	7.1—8.0 (6H, m), 7.78 (1H, dd, $J=3, 7$), 8.53 (1H, d, $J=3$)
	120—125/3	
4k	120—125/3	7.37 (1H, d, $J=4$), 7.40 (5H, s), 8.38 (1H, d, $J=4$), 8.47 (1H, s)
2l	109/20	7.17 (1H, dd, $J=4, 8$), 7.38 (1H, dd, $J=2, 8$), 8.07 (1H, dd, $J=2, 4$)
3l	46—47	6.8—7.2 (2H, m), 7.76 (1H, d, $J=2$)
4l	120—125/5	7.18 (1H, d, $J=4$), 8.10 (1H, d, $J=4$), 8.27 (1H, s)

TABLE III. Analytical Data for Chloropyridines

No.	Formulae	Analyses (%)			Found		
		Calcd					
		C	H	N	C	H	N
2d	C ₁₀ H ₁₃ ClN ₂ O	56.47	6.16	13.17	56.68	6.02	13.26
3d	C ₁₀ H ₁₃ ClN ₂ O	56.47	6.16	13.17	56.65	6.08	13.22
4d	C ₁₆ H ₁₆ ClN ₅ O ₈ ^{a)}	43.50	3.65	15.85	43.40	3.68	15.59
3f	C ₈ H ₈ ClNO ₂	51.77	4.34	7.55	51.77	4.32	7.52
2k	C ₁₁ H ₈ ClN	69.67	4.25	7.39	69.68	4.16	7.49
3k	C ₁₁ H ₈ ClN	69.67	4.25	7.39	69.80	4.16	7.36
4k	C ₁₇ H ₁₁ ClN ₄ O ₇ ^{b)}	48.76	2.65	13.38	48.82	2.86	13.36
2l	C ₇ H ₉ ClN ₂	53.68	5.79	17.89	53.68	5.57	18.10
3l	C ₇ H ₉ ClN ₂	53.68	5.79	17.89	53.79	5.91	17.77
4l	C ₁₃ H ₁₂ ClN ₅ O ₇ ^{c)}	40.48	3.14	18.16	40.37	3.12	17.97

a) Picrate, mp 144–145 °C (yellow needles from ether). b) Picrate, mp 145–147 °C (yellow needles from ether). c) Picrate, mp 164–165 °C (dec.) (yellow needles from ether).

lized from hexane–ether. Yield 170 mg (11%). The third eluate gave **2l** as a colorless liquid. Yield 30 mg (2%).

2-Chloro-3-(N,N-dimethylamino)pyridine (2l)—Acetic acid (0.5 ml) was added to a mixture of 3-amino-2-chloropyridine (640 mg, 5 mmol), 30% formaldehyde (4 ml), and NaBH₃CN (950 mg, 15 mmol) in MeCN (20 ml) during 30 min with stirring at room temperature. After 2 h, AcOH (0.5 ml) was added to the mixture during 30 min, and the mixture was stirred for 2 h. Then, 30% formaldehyde (4 ml) and NaBH₃CN (320 mg, 5 mmol) were added, and NaBH₃CN (320 mg, 5 mmol) was added twice at intervals of 30 min. The whole mixture was made alkaline with 1 N KOH and extracted with ether. The ethereal extract was washed with brine and dried over K₂CO₃. The residue obtained from the ethereal extract was purified by silica gel column chromatography using hexane–Et₃N (9:1 v/v) to give a colorless liquid. Yield 270 mg (35%).

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