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

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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 NO_2) 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]

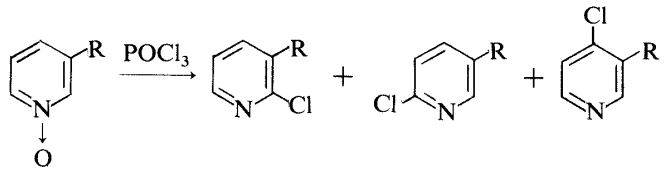
3) The reaction of 3-nitropyridine 1-oxide with phosphoryl chloride[4] gave 2-chloro-3-nitropyridine (30%) together with a small amount (8.4%) of 2-chloro-5-nitropyridine.[5]

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 (^{1}H-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



1a—l **2a—l** **3a—l** **4a—l**

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. ^{1}H-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 literature[1] 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 $POCl_3$ (10 ml), and the mixture was heated at 110 °C for 2 h. After evaporation of the excess $POCl_3$, the residue was poured onto ice, made alkaline with aqueous NH_3, and extracted with CH_2Cl_2. The CH_2Cl_2 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 $POCl_3$ (200 ml) was refluxed for 3.5 h. After evaporation of the excess $POCl_3$, the residue was poured onto ice, made alkaline with K_2CO_3, and extracted with $CHCl_3$. The $CHCl_3$ extract was purified by alumina column chromatography using C_6H_6 as an eluent. The C_6H_6 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 $POCl_3$ (200 ml) was refluxed for 5 h. After evaporation of the excess $POCl_3$, the residue was poured onto ice, made alkaline with K_2CO_3, and extracted with $CHCl_3$. The $CHCl_3$ extract was purified by silica gel column chromatography using hexane–Et_3N (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–Et_3N (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), Et_3N (10.1 g, 100 mmol), and dry dioxane (130 ml), and the mixture was stirred at −15 °C for 3 h. Then, excess Et_2NH (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, $CHCl_3$ (5 ml) and PCl_3 (550 mg, 4 mmol) were added to the residue. The mixture was refluxed for 2 h, made alkaline with 3 N Na_2CO_3, and extracted with $CHCl_3$. The $CHCl_3$ 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 $POCl_3$ (10 ml) was refluxed for 30 min. After evaporation of the excess $POCl_3$, 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 K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extract was purified by silica gel column chromatography using C_6H_6–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–Et_3N (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 (**11**) (1.37 g, 10 mmol) was treated according to the general procedure. The first eluate with C_6H_6 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 (°C) (Lit. mp or bp/mmHg)	^{1}H-NMR δ (ppm) ($CDCl_3$) ring protons
2b	105 (105—106[3])	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[7])	7.85 (1H, d, J=6), 7.97 (1H, dd, J=2, 6), 8.74 (1H, d, J=2)
4b	101—102 (102[8])	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[9])	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[10])	7.35 (1H, d, J=5), 8.55 (1H, d, J=5), 8.99 (1H, s)
2g	99—101 (96—98[4])	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[5])	7.60 (1H, d, J=8), 8.50 (1H, dd, J=2, 8), 9.29 (1H, d, J=2)
4g	154—155 (156[11])	7.56 (1H, d, J=4), 8.69 (1H, d, J=4), 9.13 (1H, s)
2h	45—46 (46—47[12])	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[13])	7.28 (1H, d, J=8), 7.82 (1H, dd, J=2, 8), 8.47 (1H, d, J=2)
4h	90/15 (22—23[14])	7.34 (1H, d, J=3), 8.36 (1H, d, J=3), 8.56 (1H, s)
2i	54—55 (55—56[15])	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[15])	7.23 (1H, d, J=8), 7.79 (1H, dd, J=2, 8), 8.49 (1H, d, J=2)
4i	115/20 (196—198[16])	7.33 (1H, d, J=5), 8.37 (1H, d, J=5), 8.73 (1H, s)
2j	193 (192—193[17])	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[14])	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[18])	7.28 (1H, d, J=5), 8.37 (1H, d, J=5), 8.46 (1H, s)
2k	46—47 110—115/3	7.20 (1H, dd, J=5, 7), 7.57 (1H, dd, J=2, 7), 8.21 (1H, dd, J=2, 5)
3k	62—63 120—125/3	7.1—8.0 (6H, m), 7.78 (1H, dd, J=3, 7), 8.53 (1H, d, J=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 (%) Calcd			Found		
		C	H	N	C	H	N
2d	$C_{10}H_{13}ClN_2O$	56.47	6.16	13.17	56.68	6.02	13.26
3d	$C_{10}H_{13}ClN_2O$	56.47	6.16	13.17	56.65	6.08	13.22
4d	$C_{16}H_{16}ClN_5O_8$[a]	43.50	3.65	15.85	43.40	3.68	15.59
3f	$C_8H_8ClNO_2$	51.77	4.34	7.55	51.77	4.32	7.52
2k	$C_{11}H_8ClN$	69.67	4.25	7.39	69.68	4.16	7.49
3k	$C_{11}H_8ClN$	69.67	4.25	7.39	69.80	4.16	7.36
4k	$C_{17}H_{11}ClN_4O_7$[b]	48.76	2.65	13.38	48.82	2.86	13.36
2l	$C_7H_9ClN_2$	53.68	5.79	17.89	53.68	5.57	18.10
3l	$C_7H_9ClN_2$	53.68	5.79	17.89	53.79	5.91	17.77
4l	$C_{13}H_{12}ClN_5O_7$[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*-dimethyamino)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 $NaBH_3CN$ (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 $NaBH_3CN$ (320 mg, 5 mmol) were added, and $NaBH_3CN$ (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 K_2CO_3. The residue obtained from the ethereal extract was purified by silica gel column chromatography using hexane–Et_3N (9 : 1 v/v) to give a colorless liquid. Yield 270 mg (35%).

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