Studies on Pyrazines. 13 [1]. Chlorination of 1-Hydroxy-2(1*H*)-pyrazinones with Phosphoryl Chloride. Formation of 2,5-Dichloro-3-phenylpyrazine from 1-Hydroxy-3-phenyl-2(1*H*)-pyrazinone

Nobuhiro Sato

Department of Chemistry, Yokohama City University,
Yokohama 236, Japan

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The chlorination of 1-hydroxy-3-phenyl-2(1*H*)-pyrazinone with phosphoryl chloride proceeded to 5-chloro-3-phenyl-2(*H*)-pyrazinone or 2,5-dichloro-3-phenylpyrazine on heating to elevated temperatures. To define the mechanism of the novel formation, reactions of the parent or methyl-substituted 1-hydroxy-2(1*H*)-pyrazinones with the same reagent were investigated.

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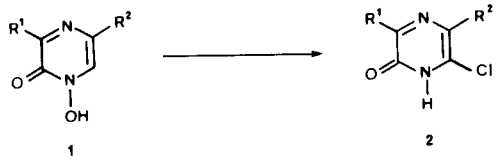
The reaction of 1-hydroxy-2(1*H*)-pyrazinones **1**, which are the hydroxamic acid form tautomers of 2-hydroxypyrazine 1-oxides [2,3], with phosphoryl chloride has a practical use for preparation of 6-chloro-2(1*H*)-pyrazinones **2** [4]. We have also shown that the synthesis of 5-phenyl substituted 6-chloro-2(1*H*)-pyrazinone **2e** proceeds by chlorination of 1-hydroxy-5-phenyl-2(1*H*)-pyrazinone (**1e**) with phosphoryl chloride [5]. During the course of our continuing research on the reaction of pyrazine *N*-oxides with phosphoryl chloride [6,7], we found a novel route to 5-chloro-3-phenyl-2(1*H*)-pyrazinone (**3**) by chlorination of 1-hydroxy-3-phenyl-2(1*H*)-pyrazinone (**1d**). The present paper reports this finding and exhaustive chlorination of several 1-hydroxy-2(1*H*)-pyrazinones **1** with phosphoryl chloride to define mechanism of the chlorination.

The starting 1-hydroxy-2(1*H*)-pyrazinones **1** were readily prepared by condensation of the corresponding α-aminohydroxamic acids and 1,2-dicarbonyl compounds [4,8]. As cited above, treatment of 1-hydroxy-3-phenyl-2(1*H*)-pyrazinone (**1d**) with phosphoryl chloride at a reflux for 1.5 hours did not give the expected 6-chloro-3-phenyl-2(1*H*)-pyrazinone (**2d**) but afforded instead the 5-chloro isomer **3** in 47% yield. The structure of **3** was confirmed by conversion into known 2,5-dichloro-3-phenylpyrazine (**4**) [9], which was reliably established by comparison of the dipole moment (0.97 D) with those of the isomeric dichloropyrazines (2.57 and 1.84 D for 2,3-dichloro-5-phenyl- and 2,6-dichloro-3-phenylpyrazines, respectively).

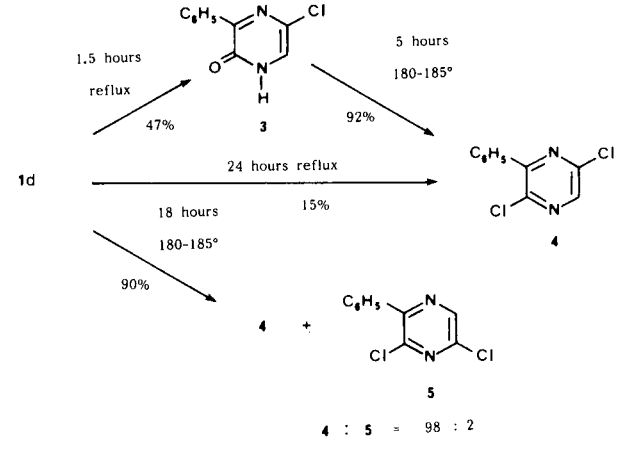


1 2

	R^1	R^2
a,	H	H
b,	CH_3	H
c,	H	CH_3
d,	C_6H_5	H
e,	H	C_6H_5

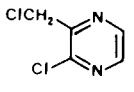
When reaction time of the chlorination of **1d** at reflux was prolonged to 24 hours, 2,5-dichloropyrazine **4** was directly formed in 15% yield. The chlorination was optimized by heating in a sealed tube at temperature of 180-185° for 18 hours, to 90% yield, contaminated with 2,6-dichloro-3-phenylpyrazine (**5**) in a ratio of 98:2. These results are summarized in Scheme I. The 2,5-dichloropyrazine **4** has

Scheme I



been made previously by a two- or three-step sequence of reactions commencing from 3-phenyl-2(1*H*)-pyrazinone in approximately 50% yields [9]. The parent and another phenyl-substituted 1-hydroxy-2(1*H*)-pyrazinones **1a** and **1e** were treated with phosphoryl chloride under the same conditions, and the yields and product ratios are summarized in Table I. In the case of methyl-substituted 1-hydroxy-2(1*H*)-pyrazinones **1b** and **1c**, the yield of dichloro products was optimized by shortening the reaction time to 3 hours. Prolonged heating resulted in a decrease of the yield due to decomposition of chlorochloromethylpyrazine **6** or **7** which was predominantly formed. The chloromethylation was almost an exclusive substitution reaction on heating **1b** and **1c** with phosphoryl chloride at reflux to give **6** and **7**, respectively. Similar predominance of side chain substitution has been observed in acetylation of

1-hydroxy-3-methyl-5-phenyl-2(1*H*)-pyrazinone and the 5-methyl-3-phenyl isomer with acetic anhydride or acetic anhydride-acetic acid [4].



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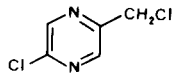

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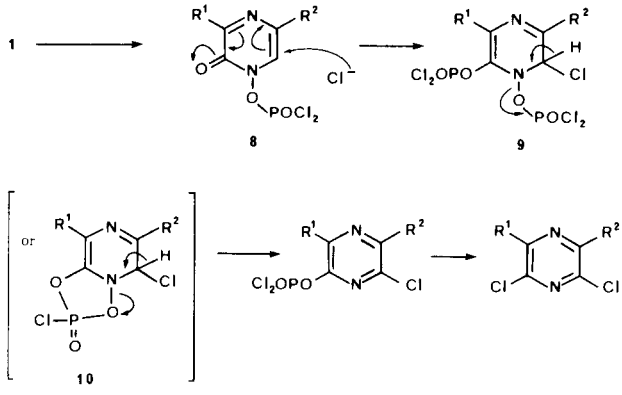
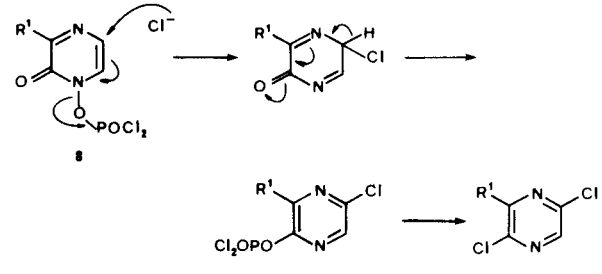
The conversion of 1-hydroxy-2(1*H*)-pyrazinones **1** into 6-chloro-2(1*H*)-pyrazinones **2** presumably involves initial formation of dichlorophosphate ester **8**, which is subsequently attacked by the chloride ion at the carbon α to the *N*-oxide function and aromatized by cleavage of the N-O bond (Scheme II). On the other hand, the intermediate **8** is

Scheme II



also susceptible to attack by chloride ion at the carbon β to the *N*-oxide function, as outlined in Scheme III. In general, heterocyclic *N*-oxides having a cyclic amide group favor nucleophilic substitution on carbon β to the *N*-oxide function [10-12]. However, the results from the

Scheme III



reactions of **1a**, **1b** and **1d** clearly indicated that the extent of β-chlorination is extremely influenced by the substituent at C-3. In contrast, the methyl or phenyl group at C-5 has little effect on proportions of dichloropyrazines. From these features in reactions, the β-chlorination in 3-substituted 1-hydroxy-2(1*H*)-pyrazinones was rationalized that formation of bisdichlorophosphate ester **9** or cyclic phosphate ester **10** is suppressed by steric hindrance of C-3 substituent, particularly the phenyl group, resulting in chlorination at the carbon β to the *N*-oxide function finally to form 2,5-dichloropyrazines.

Finally note that 2-chloro-3-phenyl- and 2-chloro-5-phenylpyrazine 1-oxides (**11**) and (**12**), which are isomers of chloro substituted 2(1*H*)-pyrazinones **2d** and **2e**, respectively, gave almost regiospecifically 2,6-dichloro-3-phenylpyrazine (**5**) by treatment with phosphoryl chloride at reflux for 2 hours (see Scheme IV and Table I).

Scheme IV

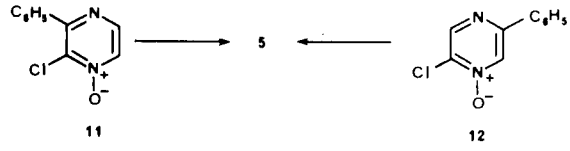


Table I

Chlorination of 1-Hydroxy-2(1*H*)-pyrazinones **1** and 2-Chloropyrazine 1-Oxides with Phosphoryl Chloride [a]

Compound	Reaction time hours	Yield %	Chlorination ratio, % (Product) positions β C-3	β C-5	α C-6	methyl
1a	18	60	15	7	78 [c]	
1b	3	67		55	45 [d]	
				17		83 (**6**)
1c	3	70	6		94 [d]	
				51		49 (**7**)
1d	18	90		98 (**4**)	2 (**5**) [f]	
11	2 [b]	91		1 (**4**)	99 (**5**) [f]	
1e	18	94	8		92 (**5**) [e]	
12	2 [b]	97	2		98 (**5**) [e]	

[a] At 180-185° unless otherwise stated. [b] At reflux. [c] Determined by glc analysis. Conditions: column 20% PEG-4000/Chromosorb WAW DMSC 2 m at 150°. [d] Column 2% OV-17/Chromosorb WAW DMCS 2 m at 100°. [e] At 175°. [f] Determined from ^{1}H-nmr spectra (deuteriochloroform).

EXPERIMENTAL

All melting points were determined on a Mel-Temp apparatus and are uncorrected. ^{1}H-nmr spectra were recorded on a JEOL JNM-MH-100 instrument with tetramethylsilane as an internal standard, and dimethylsulfoxide-d_6 was used as the solvent unless otherwise mentioned. The glc data were obtained on a Hitachi 163 gas chromatograph equipped with a digital integrator. The analytical conditions are summarized in Table I. Dipole moments were calculated by the method of Halverstadt and Kumler [13] from measurements of the dielectric constant and the specific gravity of the solvent (benzene) and four different solutions of each compound at 25°. The experimental detail was described in our previous paper [14].

1-Hydroxy-3-phenyl-2(1*H*)-pyrazinone (**1d**).

To a stirred suspension of 2-amino-2-phenylacetohydroxamic acid (16.6 g, 0.10 mole) in methanol (200 ml) and water (50 ml) was added 40% aqueous glyoxal (20 ml, 0.17 mole) at −35°. Aqueous sodium hydroxide

(2*N*, 65 ml) was then added dropwise to the mixture below −30°. The temperature was raised to 0° during 2 hours and then to 40-50° for 0.5 hour. After cooling to 10°, the mixture was acidified to *p*H 3 with 6*N* hydrochloric acid, and recooled to −20°. The precipitate was collected by filtration, and the filtrate was evaporated to dryness *in vacuo*. The residue was recrystallized from methanol to give the second crop. The combined products were recrystallized from methanol to give **1d** as yellow tiny needles (16.0 g, 85%), mp 161-163°; ^{1}H-nmr: δ 7.51 (d, H-5, 1H, $J_{5,6}$ = 4.4 Hz), 7.43-7.55 (m, aromatic, 3H), 3.05 (d, H-6, 1H), 8.3-8.42 (m, 2H).

Anal. Calcd. for $C_{10}H_8N_2O_2$: C, 63.82; H, 4.29; N, 14.89. Found: C, 63.98; H, 4.39; N, 14.63.

1-Hydroxy-2(1*H*)-pyrazinone (**1a**).

This compound was similarly prepared by condensation of glycine hydroxamic acid and aqueous glyoxal in 66% yield, mp 225-226° (from water), lit [15] mp 225-230°; ^{1}H-nmr: δ 7.35 (d, H-5, 1H, $J_{5,6}$ = 4.4 Hz), 7.97 (dd, H-6, 1H, $J_{3,6}$ = 0.8 Hz), 8.14 (d, H-3, 1H).

1-Hydroxy-3-methyl-2(1*H*)-pyrazinone (**1b**).

This *N*-oxide was similarly obtained by reaction of 2-amino-2-methylacetohydroxamic acid with aqueous glyoxal in 92% yield, mp 198-199° (from ethanol); ^{1}H-nmr: δ 2.36 (d, CH_3, 3H, J_{3,CH_3} = 0.6 Hz), 7.17 (d, H-5, 1H, $J_{5,6}$ = 4.4 Hz), 7.81 (dd, H-6, 1H).

Anal. Calcd. for $C_5H_6N_2O_2$: C, 47.62; H, 4.80; N, 22.22. Found: C, 47.63; H, 4.71; N, 22.02.

1-Hydroxy-5-methyl-2(1*H*)-pyrazinone (**1c**).

Similarly, condensation reaction of glycine hydroxamic acid and aqueous methylglyoxal afforded **1c** in 77% yield, mp 197° (from ethanol); ^{1}H-nmr: δ 2.19 (d, CH_3, 3H, J_{6,CH_3} = 0.8 Hz), 7.82 (dd, H-6, 1H, $J_{3,6}$ = 0.8 Hz), 8.06 (d, H-3, 1H).

Anal. Calcd. for $C_5H_6N_2O_2$: C, 47.62; H, 4.80; N, 22.22. Found: C, 47.32; H, 4.69; N, 22.08.

1-Hydroxy-5-phenyl-2(1*H*)-pyrazinone (**1e**).

This compound was prepared as predescribed manner by reaction of glycine hydroxamic acid with phenylglyoxal in 19% yield, mp 196-197° (from methanol), lit [8] mp 194-196°; ^{1}H-nmr: δ 7.3-7.6 (m, aromatic, 3H), 7.8-8.0 (m, 2H), 8.25 (d, H-6, 1H, $J_{3,6}$ = 0.8 Hz), 8.60 (d, H-5, 1H).

5-Chloro-3-phenyl-2(1*H*)-pyrazinone (**3**).

A mixture of **1d** (5.56 g, 0.03 mole) in phosphoryl chloride (60 ml) was stirred and refluxed for 1.5 hours, and then was condensed to one-fourth volume. The residual solution was poured into ice-water, and precipitate which formed was collected by filtration. The filtrate was extracted with chloroform (3 × 30 ml). The extract was washed with water, dried over magnesium sulfate, and evaporated to dryness *in vacuo*. The combined products were extracted with hot benzene, and the extract was evaporated to dryness. The residue was recrystallized from ethanol to give yellow crystals of **3** (2.93 g, 47%), mp 180-181°, lit [9] mp 174-176°; ^{1}H-nmr: δ 7.4-7.5 (m, aromatic, 3H), 7.88 (s, H-6, 1H), 8.2-8.3 (m, 2H).

Anal. Calcd. for $C_{10}H_7N_2ClO$: C, 58.13; H, 3.41; N, 13.56; Cl, 17.16. Found: C, 58.13; H, 3.30; N, 13.45; Cl, 17.30.

2,5-Dichloro-3-phenylpyrazine (**4**).

A mixture of **3** (1.04 g, 5.0 mmoles) in phosphoryl chloride (20 ml) was heated in a sealed tube at 180-185° for 5 hours. The solution was evaporated to dryness *in vacuo*, and the residue was treated with ice-water. The aqueous mixture was extracted with ether (3 × 50 ml), and the extract was washed with water, dried over magnesium sulfate, and evaporated to afford **4**, which was distilled at 122-123°/0.1 mm Hg (1.04 g, 92%), mp 57-58°, lit [9] mp 59-60°.

Chlorination of 1-Hydroxy-2(1*H*)-pyrazinones (**1**) with Phosphoryl Chloride at 180-185°.

A mixture of **1** (5.0 mmoles) in distilled phosphoryl chloride (9.0 ml) was heated in a sealed tube at 180-185° for the time indicated in Table I. The mixture was poured into ice-water and extracted with chloroform (20 ml + 3 × 10 ml). The extract was washed with 5% aqueous sodium hydroxide (50 ml), successively with water (2 × 100 ml), and dried over magnesium sulfate. The compositions of products in the reactions of **1** were determined by glc analysis of the chloroform extract. In the case of phenyl substituted pyrazinones, the chloroform extract was evaporated *in vacuo*, and the residue in petroleum ether (bp 80-100°) was passed through a column of Florisil (5 g). The glc analysis was carried out by using a solution of the chromatographed residue in chloroform.

2-Chloro-3- and -5-chloromethylpyrazines (**6**) and (**7**).

A mixture of **1b** or **1c** (0.632 g, 5.0 mmoles) in phosphoryl chloride (9.0 ml) was stirred and refluxed for 16 hours. The mixture was worked up in predescribed manner to give a lachrymatory oil, which was Kugelrohr-distilled at 105° (bath temperature)/22-25 mm Hg.

Compound **6** was obtained in 22% yield; ^{1}H-nmr (deuteriochloroform): δ 4.84 (d, $ClCH_2$, 2H), 8.38 (d, 1H, J = 2.4 Hz), 8.52 (d, 1H).

Anal. Calcd. for $C_5H_4Cl_2N_2$: C, 36.84; H, 2.47; N, 17.19. Found: C, 36.48; H, 2.46; N, 17.30.

Compound **7** was obtained in 19% yield; ^{1}H-nmr (deuteriochloroform): δ 4.72 (s, $ClCH_2$, 2H), 8.58 (d, 1H, J = 1.5 Hz), 8.60 (d, 1H).

Anal. Calcd. for $C_5H_4Cl_2N_2$: C, 36.84; H, 2.47; N, 17.19. Found: C, 36.73; H, 2.51; N, 17.03.

Chlorination of 2-Chloro-3- or -5-phenylpyrazine (**11**) and (**12**) with Phosphoryl Chloride.

A mixture of **11** or **12** (0.517 g, 2.5 mmoles) in phosphoryl chloride (4.5 ml) was stirred under reflux for 2 hours. The resulting solution was worked up as in predescribed manner.

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