Studies on Pyrazines. 11.[1] A Novel Formation of 2-Aminopyrazine from the Reaction of Pyrazine 1-Oxide with Phosphoryl Chloride

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Synopsis. The reaction of pyrazine 1-oxide with phosphoryl chloride gave a 49% yield of 2-chloropyrazine and a small amount of 2-aminopyrazine. The precursor of aminopyrazine was elucidated to be a 1-(2-pyrazinyl)-pyrazinium salt. The orientation of substitution in the formation of the salt was determined by reaction of deuterium labelled pyrazine *N*-oxides with phosphoryl chloride.

As part of our continuing program directed toward the reaction of pyrazine *N*-oxides,[1] we now report a novel formation of 2-aminopyrazine (**3**) from the reaction of pyrazine 1-oxide (**1**) with phosphoryl chloride.

It has been known that treatment of pyrazine 1-oxide **1** with two equivalents of phosphoryl chloride at 55 °C followed by brief reflux gives a 25% yield of 2-chloropyrazine (**2**).[2] The yield of **2**, however, was increased to 49% when **1** was treated in a large excess of the reagent at 70 °C for 2 h. Surprisingly, a small amount of 2-aminopyrazine (**3**) was isolated on hydrolytic workup of the reaction mixture. The precursor of **3** was elucidated to be a 1-(2-pyrazinyl) pyrazinium salt (**4**) from the ^{1}H NMR spectrum of the reaction mixture prior to hydrolysis (see Fig.). The doublet of doublets having the coupling constants of 4.5 and 1.5 Hz at δ 9.47 and 8.76, which correspond to C-2,6 and C-3,5 protons of the pyrazinium moeity of **4**, respectively, are characteristic for those of pyrazine 1-oxide **1** or 1-methylpyrazinium iodide.[3] Presumably the counter ion of **4** is the chloride ion but it was not established because of difficult separation of **4** from the reaction mixture. Thus, **3** was formed by decomposition of the pyrazinium group of the salt **4** under hydrolytic conditions. In addition, the NMR spectrum of the reaction mixture indicated that **2** and **4** were formed in 50% yields each. These results are illustrated in Scheme 1.

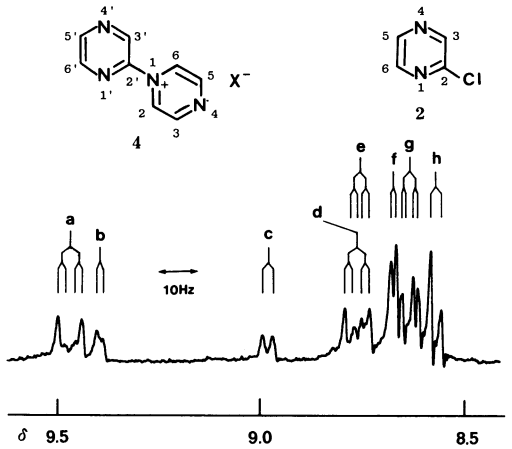
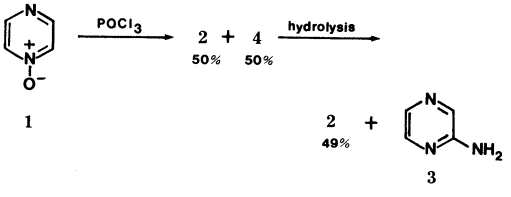


Fig. 1. The ^{1}H NMR spectrum (100 MHz) of reaction mixture formed by treatment of **1** with phosphoryl chloride at 70 °C for 2 h. Assignment of signals: a, δ 9.47, H-3,5 of **4**; b, 9.40, H-3′ of **4**; c, 8.98, H-5′ of **4**; d, 8.76, H-2,6 of **4**; e, 8.75, H-6′ of **4**; f, 8.68, H-3 of **2**; g, 8.63, H-6 of **2**; h, 8.57, H-5 of **2**. The counter ion of **4**, X^-, is chloride ion or an unidentified ion.

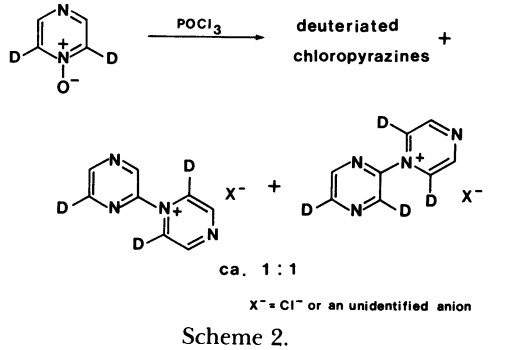
The pyrazinium salt **4** having the counter ion of $P_2O_3Cl_2^-$, which would seem to consist of several complex hydrolysates of phosphoryl chloride,[4] was isolated from the reaction mixture of **1** with phosphoryl chloride at room tempeature for 30 min. The isolated salt **4** gave satisfactory analysis for C, H, and N, and ^{1}H and ^{13}C NMR spectra. The other products of the reaction at room temperature were a 13% yield of **2**, and an approximate 30% yield of the hydrochloride of **1**.

The direction of substitution in formation of the salt **4** was significantly demonstrated by reactions of deuterium labelled *N*-oxides, pyrazine-2,6-d_2 and -3,5-d_2 1-oxides, which were obtained by treatment of the corresponding dichloropyrazine 1-oxides with deuterium. The NMR spectra of those reaction mixtures showed that the substitution reaction took place at carbons both α and β to the *N*-oxide function, and the pyrazinium nitrogen atom was derived from the nitrogen atom originally oxidized in another molecule of **1**. For example, pyrazine-2,6-d_2 1-oxide gave a pair of isomers (*ca.* 1:1) of the salts as shown in Scheme 2.

1-(2-Pyridyl)pyridinium salts have been prepared by treatment of pyridine 1-oxide with tosyl chloride in pyridine, and the hydrolysis of these salts gives aminopyridines.[5] The formation of the salt is believed to involve the nucleophilic attack of pyridine on (1-pyridinio) tosylate. The regiospecificity of the pyrazinium nitrogen of **4**, however, rules out the mechanism in which pyrazine is formed by deoxygena-



Scheme 1.



Scheme 2.

tion of the *N*-oxide **1** with phosphoryl chloride. In addition, the basicity (pK_a 0.65)[6] of the nitrogen in pyrazine is not enough to bring about the nucleophilic attack of the nitrogen atom on pyrazine *N*-phosphorodichloridate which initially formed, or chloropyrazine **2**. Actually, no incorporation of unlabelled pyrazine was observed when the reaction of deuteriopyrazine *N*-oxide was conducted in the presence of unlabelled pyrazine. We have not yet determined the mechanism which accounts for the observed regiochemistry but now the work is in progress.

Experimental

Materials. Phosphoryl chloride was used after being distilled twice at 106—107°C. Pyrazine 1-oxide (**1**) was prepared according to the procedure of Koelsch and Gumprecht.[7] The crude product was extracted with hot benzene, and the solution was passed through a column of 100/200 Florisil eluted with chloroform to remove a small amount of pyrazine 1,4-dioxide. Further purifications were carried out by sublimation at *ca.* 100°C/1 Pa and recrystallization from benzene to give **1** of mp 113—114°C (lit, 113—114°C;[7] ^{1}H NMR ($CDCl_3$): δ=8.50 (2H, dd, J=3.4 and 1.6 Hz), 8.17 (2H, dd). Deuterium labelled pyrazine 1-oxides were prepared by replacement of the corresponding dichloropyrazine *N*-oxides[8,9] (0.01 mol) in acetonitrile (50 ml) with deuterium (99.5 atom% D, 1.1 equivalents) in the presence of 5% palladium on carbon (0.1 g/1.0 g) and triethylamine (1.05 equivalents) under atmospheric pressure at 20°C. The mixture was filtered and evaporated to dryness *in vacuo*. The residue was worked up by our earlier procedure[10] to give 60—70% of the labelled *N*-oxide, which was purified by sublimation at *ca.* 100°C/1 Pa. Isotopic purity was determined by ^{1}H NMR spectrum to be 80%d_2 and 95%d_2 for pyrazine-2,6-d_2 and -3,5-d_2 1-oxides, respectively. The starting material for pyrazine-3,5-d_2 1-oxide, 3,5-dichloropyrazine 1-oxide, was prepared by N-oxidation of 2,6-dichloropyrazine with peracetic acid in acetic acid but the yield was very low (1.2—4%).[8,9] We found that the *N*-oxide was obtained in 64% yield by treatment of the dichloropyrazine with *m*-chloroperbenzoic acid (1.2 equivalents) in chloroform (reflux, 24 h).

Reaction of 1 with Phosphoryl Chloride. At 70°C for 2 h: A mixture of **1** (0.480 g, 5.0 mmol) in 9.0 ml of phosphoryl chloride was stirred and heated at 70°C for 2 h. After cooling to room temperature, the solution was poured into ice-water and basified at pH 9 with 30% aqueous sodium hydroxide. The solution was extracted with four 10-ml portions of chloroform, and the extracts were washed with two 20-ml portions of water and dried over magnesium sulfate. The yield of **2** was determined by GLC analysis of the chloroform extract.[11] The aqueous layer and washings were further basified at pH 10 with sodium carbonate and evaporated to dryness *in vacuo*. The residue was sublimed at 100°C/1 Pa to give 0.026 g (11%) of **3**, mp 114—116°C. This compound was identified by comparison with the IR and NMR spectra of the authentic sample, mp 119—120°C, purchased from Aldrich Chem. Co.

At Room Temperature: A mixture of **1** (0.480 g, 5.0 mmol) in 9.0 ml of phosphoryl chloride was stirred at room temperature for 30 min, and then 20 ml of dry chloroform was added to the mixture. Insoluble material was collected by filtration and the filtrate was worked up as described. The insoluble material was dried at room temperature *in vacuo* and triturated in dry nitromethane. Insoluble material (hydrochloride of **1**, 0.2 g, 30%; Found: C, 35.73; H, 3.67; N, 21.13; Cl, 26.97%. Calcd for $C_4H_5N_2OCl$: C, 36.24; H, 3.80; N, 21.14; Cl,26.75%) was collected by filtration, and dry carbon tetrachloride was added to the filtrate to give 0.44 g of **4**. Several purifications in the predescribed fashion gave an unstable solid of **4**, mp 126—128°C (decomp); IR (KBr): 1606 cm^{-1} (P=O); ^{1}H NMR (nitromethane-d_3): δ=9.51 (2H, dd, J=4.5 and 1.5 Hz), 9.41 (1H, d, J=1.5 Hz), 9.02 (1H, d, J=2.6 Hz), 8.84 (2H, dd, J=4.5 and 1.5 Hz), 8.80 (1H, dd, J=2.6 and 1.5 Hz); ^{13}C NMR (nitromethane-d_3): 149.5, 145.2, 141.4 (C-3′, 4′, 5′), 147.3 (C-2′), 139.0, 138.7 (C-2,6 and C-3,5); Found: C, 28.30; H, 2.38; N, 16.69; Cl, 19.46%. Calcd for $C_8H_7N_4P_2O_3Cl_2$: C, 28.26; H, 2.08; N, 16.48; Cl, 20.85%.

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