DIAZOTIZATION OF SOME AMINODIAZINE N-OXIDES

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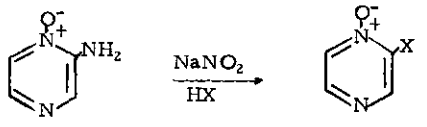
Abstract - Diazotization of a number of aminopyrazine and aminopyrimidine N-oxides affords intermediate diazonium compounds which can be converted to the corresponding bromo and chloro analogs in the presence of the appropriate halide ions. In some instances, electrophilic aromatic substitution takes place prior to the diazotization step. Nucleophilic halogenation accompanying deoxygenation occurs with 2-aminopyrimidine N-oxide in the same manner as described for some 3-amino-1,2,4-triazine 2-oxides.

The diazotization of the four possible aminopyridazine N-oxides has been described.[1,2] Except for the 3-amino isomer, the corresponding halo derivatives are obtained in high yields. The diazotization of 3-amino-1,2,4-triazine 1- and 2-oxides[3,4] affords the corresponding halo derivatives as well. The diazotization of 3-amino-1,2,4-triazine 1-oxide also yields an electrophilic ring-substitution product, the 3,6-dibromo-1,2,4-triazine 1-oxide.

The diazotization of 3-aminopyrazine 1-oxide has been described as affording the corresponding 1-hydroxy-1,2-dihydropyrazinone.[5] In view of these results, a diazotization study of other aminodiazine N-oxides seemed appropriate. Now we report the results of these studies.

The diazotization of 2-amino-(1) and 3-aminopyrazine 1-oxide (2) using a hydrohalic acid and sodium nitrite afforded the corresponding mono-halo N-oxides (3, 4, 5, 6). These results differ from the reported formation of 3-oxo-3,4-dihydropyrazine 1-oxide, when the diazotization is done in dilute sulfuric acid.[5]



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3: X = Cl

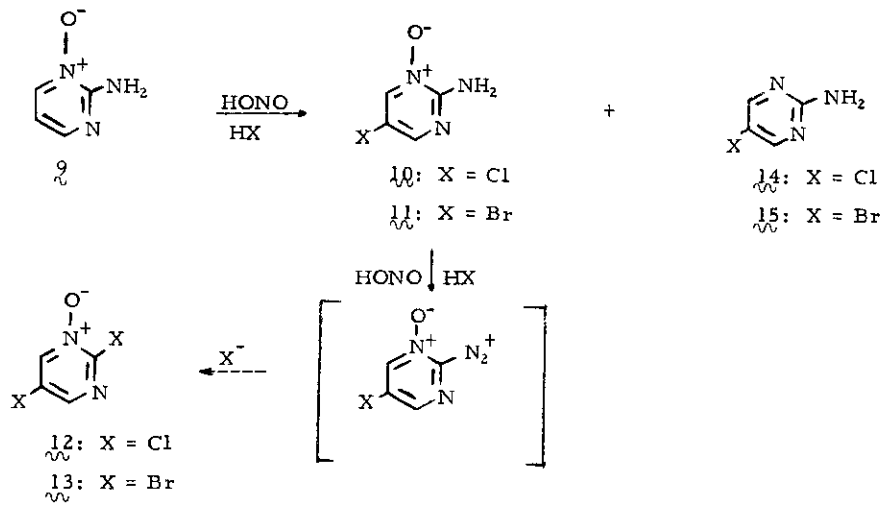
4: X = Br

2 5: X = Cl 6: X = Br 7: X = Br 8

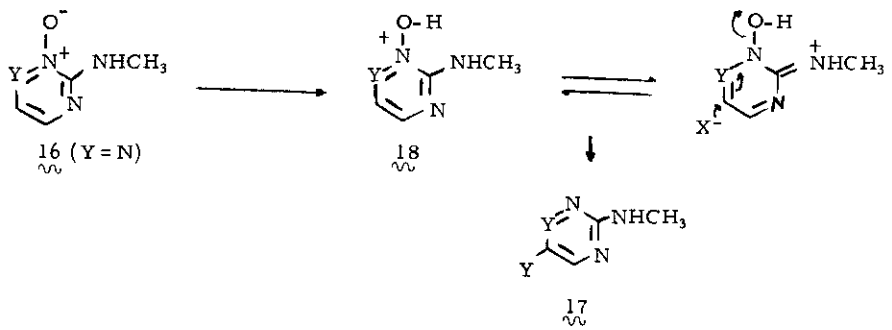
In the case of 3-aminopyrazine 1-oxide (2), 2,3,6-tribromopyrazine 1-oxide (7) is isolated as well as 3-bromopyrazine 1-oxide (6). The formation of compound 7 is expected in view of the *facile* bromination of 3-aminopyrazine 1-oxide, which we have recently described.[6] Consequently, compound 7 is most probably formed by diazotization of 2,6-bromo-3-aminopyrazine 1-oxide (8). The formation of compound 7 follows the same pattern as we have already described in the halogenative diazotization of 3-amino-1,2,4-triazine 1-oxide, where 3,6-dibromo-1,2,4-triazine 1-oxide is formed.

The diazotization of 2-aminopyrimidine 1-oxide (9) does not appear to have been reported. When this compound is diazotized under the same conditions as the aminopyrazine N-oxides, the initially formed compounds are the 2-amino-5-halopyrimidine 1-oxides (10, 11). These compounds are, ultimately, transformed to the 2,5-dihalopyrimidine 1-oxides (12, 13). The initial formation of the 2-amino-5-halopyrimidine 1-oxides (10, 11) has precedent in our earlier publication describing the direct halogenation of compound 9.[6] The yields of compounds 12 and 13 are increased considerably by the addition of sodium bromide and sodium chloride, respectively, to the diazotization medium.

Of additional interest is the observation that the 2-amino-5-halopyrimidines 14 and 15 are also isolated from these reactions. The formation of these compounds follows the pattern observed in the 3-amino-1,2,4-triazone 2-oxide, where the 3-amino-6-halo-1,2,4-triazines are obtained when these compounds are treated with hydrohalic acids, and in the nitrosation of 3-amino-1,2,4-triazine 1-oxide, where the corresponding 3,6-dibromo-1,2,4-triazine 1-oxide is formed.[4]



It was reported that the treatment of 3-alkylamino-1,2,4-triazine 2-oxides (16, Y = N) with hydrohalic acids affords the corresponding 6-halo-3-alkylamino-1,2,4-triazine (17, Y = N). The mechanism involved in this transformation proceeds by nucleophilic attack of X^- on the protonated 2-oxides (18, Y = N).[3,4]



The same mechanism can be invoked to account for the formation of compounds 14 and 15.

The formation of compounds 7, 10, 11, 12, and 13 can be rationalized by the observations that electrophilic halogenation of 3-aminopyrazine 1-oxide (2) affords 2,6-dihalo-3-aminopyrazine 1-oxide, and halogenation of 2-aminopyrimidine 1-oxide generates 2-amino-5-halopyrimidine 1-oxide.[6] These halogenated products are the result of electrophilic substitution. In order to account for these electrophilic substitution products in the diazotization reaction using hydrohalic acids, the formation of X^+ (or of its possible precursor, X_2) is required. Nitrous acid, an oxidizing agent, could account for the formation of these species ($2\,NO_2^- + 2\,X^- + 4\,H^+ = 2\,NO + X_2 + 2\,H_2O$). Some precedent in heterocyclic chemistry of this type of reaction is known. N-oxidation, with peracetic acid, of a number of halogenated pyrimidines yields 5-chloro derivatives by hydrolysis of a

4-chloro substituent, serving as the initial Cl^- source. The oxidizing agent, in this instance peracetic acid, generates the required Cl^+ species.[7,8]

CONCLUSIONS

1) Diazotization of aminopyrazine and aminopyrimidine N-oxides with sodium nitrite and a hydrohalic acid affords intermediate diazonium compounds which are converted to the corresponding bromo- and chloro- analogs in the presence of the appropriate halide ions.

2) Prior to the diazotization step, electrophilic substitution with X^+ species, made by HONO acting as an oxidizing agent upon HX, occurs at the same sites as direct halogenation in the corresponding aminodiazines. Thus, the presence of the N-oxide group in these compounds does not alter the electrophilic substitution behavior of named aminodiazines.

3) Nucleophilic halogenation with deoxygenation, as already noted for some 3-substituted 1,2,4-triazine N-oxides, occurs in the diazotization of 2-aminopyrimidine N-oxide.

EXPERIMENTAL

The proton nmr spectra were recorded with a Varian HA-100 spectrometer. Mass spectra were obtained for all reaction products with a Hitachi Perkin-Elmer RMU-6M instrument equipped with a solid sample injector. The ionizing voltage was 70 eV. The molecular weights of all of the reported products are in agreement with the assigned structures. Elemental analyses were determined by the Analytical Services Laboratory of the University of Alabama, Dept. of Chemistry.

Preparation of 2-Bromopyrazine 1-Oxide (4). A mixture of 110 mg (1.0 mmol) of 2-aminopyrazine 1-oxide (1) and 1.0 ml of 47% hydrobromic acids with 0.3 ml of water were stirred at room temperature until a clear red solution was obtained (about 35 min). To this solution was added, dropwise (under cooling, NaCl-ice bath), 0.5 ml of water containing 120 mg (1.7 mmol) of $NaNO_2$. The addition was completed within 15 min with continuous stirring. The whole was slowly brought to room temperature (15 min), left standing for 10 min at 22°C, and partially neutralized with saturated aqueous $NaHCO_3$ (pH=4.5). The resulting solution was extracted with CH_2Cl_2 (5 x 5 ml). The combined CH_2Cl_2 extracts were dried over anhydrous Na_2SO_4, filtered, and the solvent was evaporated to dryness under reduced pressure (70 torr) to yield a white solid, which was sublimed at 55°C/0.05 torr to give 93 mg (0.53 mmol) of 4 (53%), mp 126-127°C.

2-Chloropyrazine 1-oxide (3) was prepared by a similar procedure in 33% yield, mp 130-132°C (Lit. 133-134°C).[9]

Preparation of 3-Chloropyrazine 1-oxide (5). A mixture of 525 mg (4.73 mmol) of 3-aminopyrazine 1-oxide (2) and 5.0 ml of 40% HCl was stirred at room temperature until the amine (2) had completely dissolved. To this clear solution was added, dropwise (under cooling, NaCl-ice bath), 2.0 ml of H_2O containing 670 mg (9.71 mmol) of $NaNO_2$. The addition was completed within 45 min and was accompanied with continuous stirring. The mixture was slowly brought to room temperature (20 min), left standing for 15 min at 22°C, and partially neutralized with saturated aqueous $NaHCO_3$ (pH=4.5). The resulting solution was extracted with CH_2Cl_2 (5 x 25 ml) and the combined CH_2Cl_2 extracts were dried over anhydrous Na_2SO_4, filtered, and the solvent was evaporated to dryness under reduced pressure (70 torr) to yield a white solid. It was sublimed at 60°C/0.05 torr to give 263 mg (2.0 mmol) of 5 (42.6%), mp 94-95°C (Lit. 95-96°C).[10]

Reaction of 3-Aminopyrazine 1-Oxide (2) with $NaNO_2$/HBr. To 444 mg (4.0 mmol) of 2 was added 6.0 ml of 47% HBr. The yellow solution was cooled to 5°C and 552 mg (8.0 mmol) of $NaNO_2$ in 2.0 ml of water was added dropwise (15 min). After stirring for 15 min at room temperature, 10.0 ml of $CHCl_3$ was added. The reaction was worked up as above to give 278 mg of 3-bromopyrazine 1-oxide (6) in 39.7% yield and 104 mg of 2,3,6-tribromopyrazine 1-oxide (7) in 7.8% yield. Both 6 and 7 were further purified by vacuum sublimation.

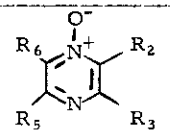
Reaction of 2-Aminopyrimidine 1-Oxide (9) with $NaNO_2$/HBr. In a typical experiment, 276 mg (4.0 mmol) of $NaNO_2$ in 1.0 ml of water was added dropwise (20 min) to a solution of 222 mg (2.0 mmol) of compound 9 in 1.7 ml of 47% HBr cooled to -5°C. After the addition was complete, 10 ml of $CHCl_3$ was added and the cold reaction mixture was brought to room temperature. After 10 min, the $CHCl_3$ layer was separated and additional $CHCl_3$ (4 x 10 ml) extractions were made. The combined $CHCl_3$ extracts were dried over Na_2SO_4, filtered, and evaporated in vacuo. The light yellow residue was sublimed at 95°C/0.05 torr to give 115 mg of 5-bromo-2-aminopyrimidine 1-oxide 11 in 30% yield. An additional product, 2-amino-5-bromopyrimidine (15) was detected in the aqueous reaction mixture and extracted with ethyl acetate/12% methanol. It was sublimed at 110°C/0.05 torr to give 93 mg of 15 (26.7%), mp 242-244°C (Lit. 242-244°C).[11]

Reaction of 2-Aminopyrimidine 1-Oxide (9) with $NaNO_2$/HCl. The procedure was the same as above except that hydrochloric acid was substituted for HBr. The major product was deoxygenated 9. It was isolated in 34% yield together with some 5-chloro-2-aminopyrimidine 1-oxide (10) in 6% yield and 2-amino-5-chloropyrimidine (14) in 8.5% yield, mp 236-238°C (Lit. 236-237°C).[11]

Reverse Addition Diazotization of 2-Amino-5-Halopyrimidine 1-Oxides (10, 11). Into a 25-ml, three-neck flask, equipped with a magnetic stirrer, dropping funnel, and thermometer, were added 0.8 ml water, 900 mg NaBr, 300 mg (4.28 mmol) $NaNO_2$, and 372 mg (2.14 mmol) 2-amino-5-bromopyrimidine 1-oxide (11). After the mixture was cooled to -10°C, 0.48 ml (4.28 mmol) of concentrated hydrobromic acid was added dropwise over a period of 20 min. Since the heat of reaction is high, the temperature range must be kept at -3° to -10°C by external cooling. An additional reaction time of 10 min was allowed, after which time air was bubbled through the solution to remove bromine and any oxides of nitrogen. The solution was made alkaline (pH=8.0) with 4% NaOH, filtered, and the filtrate and residue each were extracted with four 5.0-ml portions of CCl_4. The combined extracts were allowed to evaporate at room temperature. The yield of crude 2,5-dibromopyrimidine 1-oxide (13) was 147 mg (0.59 mmol, 27%). This solid was recrystallized twice from petroleum ether and sublimed.

2,5-Dichloropyrimidine 1-oxide (12) was prepared by a similar procedure, in 16% yield.

TABLE I. Analytical Data for Some Pyrazine 1-Oxides[a]



Cmpd	Molecular Formula	mp, °C[b]	Substituents				^{1}H nmr chemical shifts[c,d]				Coupling Const. (Hz)	
			R_2	R_3	R_5	R_6	R_2	R_3	R_5	R_6	$J_{2,6}$	$J_{5,6}$
4	$C_4H_3N_2OBr$	126-127	Br	H	H	H	-	8.79	8.42	8.29	-	4.0
3	$C_4H_3N_2OCl$	130-131	Cl	H	H	H	-	8.62	8.36	8.22	-	4.0
6	$C_4H_3N_2OBr$	95-95	H	Br	H	H	8.23	-	8.32	8.09	1.5	4.0
5	$C_4H_3N_2OCl$	95-96	H	Cl	H	H	8.12	-	8.22	7.96	1.5	4.0
7	$C_4HN_2OBr_3$	149-150	Br	Br	H	Br	-	-	8.50	-	-	-
8[e]	$C_4H_3N_3OBr$	215-216	Br	NH_2	H	Br	-	-	8.70	-	-	-

a. For all compounds elemental analyses were within ±0.3% of the calculated value.

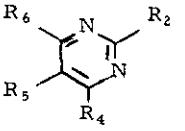
b. Melting points were taken on a Thomas-Hoover melting point apparatus.

c. All spectra were recorded as dilute solutions in $CDCl_3$ except where otherwise indicated.

d. δ(ppm) downfield from TMS.

e. d_6-DMSO

TABLE II. Analytical Data for Some Pyrimidines and Their 1-Oxides[a]



Cmpd	Molecular Formula	mp, °C[b]	Substituents				^{1}Hnmr chemical shifts[c, d]				Coupling Constants (Hz)
			R_2	R_3	R_5	R_6	R_2	R_3	R_5	R_6	$J_{4,6}$
11[e]	$C_4H_4N_3OBr$[f]	234-236	NH_2	H	Br	H	8.24	9.13	-	8.36	2.0
10	$C_4H_4N_3OCl$[f]	218-219.5	NH_2	H	Cl	H	8.50	9.05	-	9.30	2.0
13	$C_4H_2N_2OBr_2$[f]	106-107	Br	H	Br	H	-	9.33	-	9.54	2.0
12	$C_4H_2N_2OCl_2$[f]	101.5-102	Cl	H	Cl	H	-	9.27	-	8.41	2.0
15[e]	$C_4H_4N_3Br$	242-244	NH_2	H	Br	H	8.40	8.75	-	8.75	-
14[e]	$C_4H_4N_3Cl$	236-238	NH_2	H	Cl	H	8.35	8.70	-	8.70	-

a. For all compounds elemental analyses were within ±0,3 % of the calculated values.

b. Melting points were taken on a Thomas-Hoover melting point apparatus

c. All spectra were recorded as dilute solutions in $CDCl_3$ except where otherwise indicated.

d. δ (ppm) downfield from TMS.

e. d_6-DMSO.

f. N_1-Oxide

Elemental Analyses:

Compound	Molecular Formula	Calculated			Found		
		%C	%H	%N	%C	%H	%N
4	$C_4H_3N_2OBr$	27.45	1.73	16.01	27.26	1.82	15.88
6	$C_4H_3N_2OBr$	27.45	1.73	16.01	27.44	1.61	16.21
7	$C_4HN_2OBr_3$	19.00	0.40	11.08	18.89	0.38	10.94
10	$C_4H_4N_3OCl$	33.00	2.78	28.87	33.18	2.86	28.56
11	$C_4H_4N_3OBr$	25.28	2.13	22.12	25.27	2.09	21.83
12	$C_4H_2N_2OCl_2$	29.12	1.22	16.98	29.03	1.17	17.00
13	$C_4H_2N_2OBr_2$	18.92	0.80	11.04	18.87	0.75	10.96

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Received, 9th May, 1983